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INSULIN RESISTANCE*

Report of a Case

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THE knowledge that by the intelligent use of insulin combined with dietary regulation almost all cases of diabetes mellitus can be satisfactorily controlled affords the physician considerable peace of mind. However, it is important to remember that the fundamental metabolic defect in this disease is still a subject of controversy, and that since the discovery of insulin little has been learned of the mechanism by which it effects the oxidation of dextrose. This fact is forcibly brought to one's attention when one encounters a patient who exhibits the phenomenon variously designated as "insulin resistance" and as "insulin antagonism." The consensus is that the former term may be used when a patient requires more insulin than the clinical character of his disease seems to demand, especially when amounts in excess of 100 or 150 units are taken daily for considerable periods without insulin reactions, or without obtaining the expected effect on the blood sugar or glycosuria. In most cases of diabetes when the patient requires between 100 and 150 units, a responsible complication can almost invariably be disclosed, and even so, the total daily dose rarely exceeds 150 units. When larger dosages are required, or when the explanation available for high requirements is inadequate, the condition is properly called "insulin resistance."

CASE REPORT

A 53-year-old accountant who lived in Alaska registered at the Mayo Clinic on August 12, 1938, complaining of a slight loss of weight, an occasional tired feeling and periodic polydipsia and polyuria. His father had died of diabetes mellitus at the age of 78.

In July, 1937, the patient had an attack of influenza and was confined to bed for 2 or 3 days because of fever, weakness, nausea, vomiting and sharp pain in the pit of the stomach. He recovered shortly but felt worn out. Two weeks later he had a similar attack and remained in bed for 10 days. At his own suggestion a urinalysis was performed, and the presence of diabetes mellitus was discovered. He was placed on a diet and went for treatment to Seattle, where, after a complete examination, he was placed on a diet of 200 gm. of carbohydrate, 80 gm. of protein and 100 gm. of fat, and instructed to take 30 units of insulin daily (protamine insulin, 20 units; regular insulin, 10 units). For several months the symptoms were allayed but he made no gain in weight. Although the food was weighed, the patient often failed to fulfill his dietary requirements.

He performed his own urinalyses four times daily, and in January, 1938, again noted sugar in the urine. At this time he began to feel weakness, particularly in the lower part of the back; this was associated with pain. At times he was unable to climb stairs. In February, 1938, a physician discontinued the use of the Joslin diet, placed him on a low-carbohydrate, high-fat diet, and increased the daily dose of insulin to 45 units (protamine insulin, 30 units; regular insulin, 15 units), but sugar still persisted in the urine. The patient remained on the diet but gradually increased the dosage of insulin until during the first week in August, 1938, he was taking 96 units per day (protamine insulin, 64 units; regular insulin, 32 units). Despite the large amounts of insulin taken, he excreted sugar in the urine continuously for 8 months. Two weeks before coming to the clinic he returned to the Joslin diet. For 6 months he had no major illnesses, colds or other symptoms, but he became progressively weaker and lost 16 pounds.

During the preceding 10 years he had had several attacks of indigestion. In August, 1937, he had an attack of pain in the right side of the epigastrium. The distress did not disappear as it had before, but persisted for a week and was associated with nausea and vomiting. There was no history of jaundice or intolerance to fatty foods. In July, 1938, five teeth were removed. For a few months before the patient came to the clinic he was somewhat dyspneic on exertion. The appetite was good.

On physical examination the patient appeared thin, emaciated and ill. His height was 69 inches (175.3 cm.), and his weight 132 pounds. His normal weight was 148 pounds, and he had weighed 175 pounds 2 years previously. The skin was dry and somewhat icteroid. The eyes, ears, nose and throat were essentially normal. There was evidence of recent extraction of teeth. The heart and lungs were normal. The abdomen was scaphoid. There

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were no palpable masses. The prostate gland was somewhat enlarged. There were marked varicosities in both legs, with some pigmentation on the shins. The peripheral arteries were moderately thickened and tortuous; their pulsations were good. The reflexes were normal.

Because the patient's urine contained acetone and diacetic acid, he was sent to the hospital, where the examination was completed. The concentration of hemoglobin and the red-cell count were normal. The white-cell count was 5000. The sedimentation rate was normal — 7 mm. at the end of 1 hour. Roentgenologic examination of the thorax disclosed no abnormality, and a roentgenogram of the gall bladder revealed a non-functioning organ. The results of the Kline, Kahn, Hinton and Kolmer tests on the blood serum were negative. Dental examination revealed moderate periapical infection and pyorrhea. Removal of the upper second molar tooth on the right side was advised. Examination of the ear, nose and throat revealed moderate septal deflection. The tonsils showed minimal evidence of infection. The pupils reacted promptly to light and accommodation. The ocular fundi appeared normal. There was no evidence of infection of the prostate gland. The basal metabolic rate on different days was –9 and –3 per cent. The liver-function test revealed no retention of the dye. The concentration of serum bilirubin was 1.0 mg. per 100 cc., and the van den Bergh reaction was indirect. The electrocardiogram showed sinus arrhythmia and low amplitude of T waves in Leads 2 and 3. Examination of a biopsied section of skin disclosed no evidence of hemochromatosis.

On admission to the hospital the patient was placed on a standard diabetic diet, which consisted of 147 gm. of carbohydrate, 75 gm. of protein and 147 gm. of fat. The value for the fasting blood sugar the next morning was 306 mg. per 100 cc., and the carbon dioxide combining power of the plasma was 59.8 vol. per cent. The patient continued to excrete large amounts of sugar in the urine, with traces of acetone and diacetic acid. The insulin requirement rose rapidly, until it was necessary to give 300 units daily; even then, marked glycosuria was present.

There was very little local reaction at the site of injection of the insulin. However, insulin was given intravenously for 6 days. The requirement continued to rise steadily under this regime (Fig. 1).

The concentration of chlorides was 617 mg. per 100 cc. of plasma; the value for the sodium was 311 mg. per 100 cc. of serum, and that for the potassium was 20 mg. per 100 cc. Although the concentration of plasma chlorides approached the upper normal limit, large amounts of sodium chloride were given, since the procedure had previously been found helpful in some cases of insulin resistance.[1] Two thousand cubic centimeters of a 2 per cent solution of sodium chloride was given daily by mouth for 2 weeks. In 4 days the insulin requirement fell from 300 to 220 units, and on the 5th day it rose to 270 units. It was then decided to place the patient on a diet low in potassium, that is, one that supplied from 1.2 to 2.0 gm. of potassium daily. As shown in Figure 1, the insulin requirement fell to 180 units in 7 days and then began to rise. On August 29, 1938, the concentration of potassium was 31 mg. per 100 cc. On the low-potassium diet the concentration of serum potassium fell. On September 1 it was 22 mg. per 100 cc. and on September 5 20 mg.

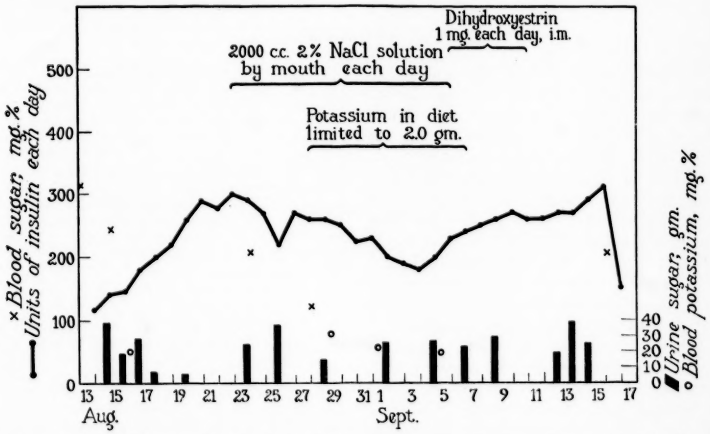

FIGURE 1. *Insulin Requirements in a Case of Insulin Resistance, and the Effect Thereon of Administration of Sodium and Potassium.*

Large doses of female sex hormone — 10,000 units of dihydroxyestrin — were given intramuscularly for 4 days. The insulin requirement, however, continued to rise.

There seemed to be no explanation for the insulin resistance except a possible pancreatitis secondary to chronic cholecystitis, which was indicated by the history and the roentgenologic report of a non-functioning gall bladder. No lipase was present in the serum. There were 106 units of amylase in each 100 cc. of serum. However, cholecystectomy was advised.

On September 15 a cholecystectomy and an exploratory choledochostomy were performed. Manual examination

of the pancreas failed to reveal any abnormality, and there seemed to be practically no induration of the pancreas. The liver showed a slight degree of hepatitis, as evidenced by some rounding of the edge and slight scarring in the region near the fundus of the gall bladder. The common bile duct was about three times the normal size, and in order to be sure nothing abnormal was present to afford prolonged drainage of the biliary tract, a small longitudinal incision was made in it. A small quantity of clear bile and a few bits of flaky material escaped. The pathologist's report was as follows: "Gall bladder: chronic cholecystitis with thickened and slightly infiltrated walls; cholelithiasis, multiple stones (largest 1.5 cm., smallest 3.0 mm.). Regional lymph node: inflammatory." A culture taken from the gall bladder revealed a few gram-negative bacilli.

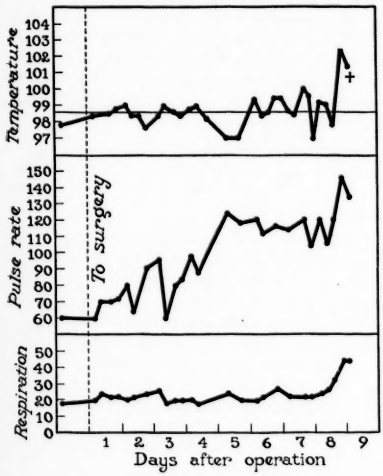

FIGURE 2. *Temperature, Pulse and Respirations after Operation in a Case of Insulin Resistance.*

Following operation the patient got along very well for the first 3 days. The temperature did not exceed 99°F., the pulse rate did not go above 96, and the respirations remained about normal (Fig. 2). The daily insulin requirement gradually rose to 300 units (Fig. 3). On the 4th day after operation urinalysis revealed a marked glycosuria, and considerable acetone and diacetic acid. The skin was dry, and there was an acetone odor to the breath. Since the patient had not eaten much, 2000 cc. of a 5 per cent solution of dextrose was given intravenously, along with 20 units of insulin. The concentration of blood sugar was 298 mg. per 100 cc. During the night he became irrational, vomited several times and complained of pain in the epigastrium. The next morning respirations were rapid, the mouth was dry and the breath had the odor of acetone. At this time the concentration of the blood sugar was 492 mg. per 100 cc. and the carbon dioxide combining power of the plasma 15.5 vol. per cent. Gastric lavage was employed, and 100 cc. of a 5 per cent solution of sodium bicarbonate was left in the stomach. Two thousand cubic centimeters of a 0.9 per cent solution of sodium chloride containing 200 units of insulin was given intravenously. At 8 a.m. the value for the blood sugar was 572 mg. per 100 cc. and the carbon dioxide combining power of the plasma 12.6 vol. per cent. At 11 a.m. the concentration of blood sugar was 600 mg., and the carbon dioxide combining power of the plasma 10.7 vol. The patient was then given 500 cc. of a 5 per cent solution of sodium bicarbonate intravenously and placed on a regime of 100 units of insulin per hour. Respirations became less rapid, and the pain in the epigastrium diminished. The patient became much clearer mentally and was given another 500 cc. of a 5 per cent solution of sodium bicarbonate during the afternoon. At 7 p.m. the value for the blood sugar was 353 mg., and the carbon dioxide combining power of the plasma 32.4 vol. At 2 a.m. the next day (the 5th day after operation) urinalysis disclosed moderate glycosuria, and only a trace of acetone. The dose of insulin was then decreased to 40 units per hour. At 8 a.m. the concentration of blood sugar had decreased to 22 mg. and the carbon dioxide combining power of the plasma had increased to 61.7 vol. The patient was drowsy and unable to drink. He was given 20 cc. of a 50 per cent solution of dextrose intravenously, and this was followed by the intravenous administration of 1000 cc. of a 5 per cent solution of dextrose in physiologic saline solution. The patient then felt much better.

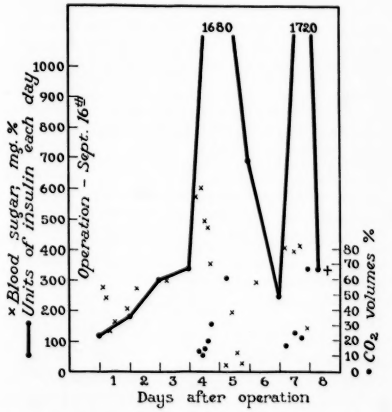

FIGURE 3. *Insulin Requirement after Operation in a Case of Insulin Resistance.*

At 11 a.m. of the 5th day after operation, the value for the blood sugar was 197 mg. One hundred and sixty units of insulin was given at 1 p.m. At 4 p.m. the concentration of the blood sugar was 68 mg. The dose of insulin was decreased from 100 to 50 units and was administered every 3 hours. The patient became rather drowsy and thirsty. At 9 p.m. the value for the blood sugar was 26 mg., and 20 cc. of a 50 per cent solution of dextrose was given intravenously. The urine was free of sugar. The dose of insulin was then decreased from 50 to 25 units and was repeated every 3 hours. The urine remained free of sugar during the night. At 8 a.m. of the 6th

day after operation the value for the blood sugar was 291 mg. and urinalysis disclosed a moderately severe glycosuria and traces of acetone and diacetic acid. The patient gradually went into acidosis in spite of increasing doses of insulin. At 8 a.m. of the 7th day after operation the carbon dioxide combining power of the plasma was 17.4 vol. per cent. The skin was dry and respirations were of the Kussmaul type. A total of 1720 units of insulin was given, along with 1500 cc. of a 5 per cent solution of sodium bicarbonate and 3500 cc. of a 0.9 per cent solution of sodium chloride intravenously. At 11:30 p.m. the patient seemed to be in surprisingly good condition, rational and able to take fluids. The concentration of the blood sugar was 140 mg., and the carbon dioxide combining power of the plasma was 67 vol. At 12:30 a.m. of the 8th day after operation the patient's condition suddenly changed. Respirations became of the Cheyne–Stokes type; the systolic blood pressure ranged from 78 to 84, the diastolic from 52 to 56 mm. The pulse rate ranged from 148 to 160; the pulse was thready, and there was great variation in the strength of the beats. The patient soon became irrational. Dextrose and Ringer's solution were administered intravenously, but the blood pressure continued to fall. The patient died at 5:30 a.m.

Necropsy revealed recent bilateral bronchopneumonia with several small recent abscesses in the right lung. There was a moderate degree of generalized atherosclerosis. The common bile duct was twice the normal size. Its wall was thickened, there was evidence of subacute inflammation in the mucosa, and some inflammatory cells were present in the surrounding tissue. The liver was normal in color and consistence, and was not enlarged; on microscopic examination it appeared normal. The pancreas appeared grossly normal. Microscopic examination revealed an occasional abnormal-looking island of Langerhans in the head, and hyalinization of the islands in the tail. There was a small fetal adenoma in the left lobe of the thyroid gland. The thymus had been almost completely replaced by fat. The suprarenal glands, testes, kidneys, prostate gland and pituitary body appeared normal on both gross and microscopic examinations.

Comment

Cases of extreme resistance to insulin such as this are fortunately unusual. By far the most spectacular is one reported by Wiener.[2] The patient, a man aged fifty-eight years, required as much as 3250 units of insulin in twenty-four hours. Wiener made attempts to determine the presence of a contrainsular hormone by injecting the patient's serum into rabbits and noting the effect on the concentration of blood sugar, but the results were negative.

Glen and Eaton[3] report a case of diabetes in which the patient, a woman, aged forty-six, required from 900 to 1050 units of insulin daily for twenty-seven days without appreciable effect on the blood sugar or the glycosuria. Her diabetes had begun eight years previously, following the removal of the uterus and an ovary. The insulin requirement rose gradually from the onset of the disease until her death in coma. Glycosuria, thirst and pruritus persisted in spite of the increasing dose, although there was practically no ketonuria. The basal metabolic rate varied from +49 to +16 per cent during the last two years of her illness, yet there was no clinical evidence of hyperthyroidism. When insulin was given with dextrose, the dextrose tolerance was less than when no insulin was given. When the administration of insulin was stopped, ketosis rapidly developed. The injection of dihydroxyestrin increased the dextrose tolerance and also relieved the pruritus. The parenteral administration of phosphates lowered the concentration of blood sugar for a short time. The injection of the patient's serum along with insulin into rabbits markedly diminished the hypoglycemia produced by insulin. This effect was still more marked if the patient had received insulin before the serum was withdrawn.

Watson and Dick[4] in 1933 described an experiment that indicated the presence of a substance in the urine of diabetic patients that causes partial inactivation of insulin.

De Wesselow and Griffiths[5] report that the injection of blood plasma of some elderly, obese glycosuric patients into rabbits diminished the hypoglycemic action of insulin. The plasma of young diabetic patients gave negative results.

Fitz[6] suggests that some agent is present in the blood and tissues that, in a more direct way than has been suggested, may oppose or neutralize the action of insulin, or that some enzyme needed for activation of insulin, such as an insulin kinase, is deficient because of a defect of the pancreas or liver.

Greene and Thatcher[7] recently reported a case of resistance to protamine-zinc insulin without resistance to regular insulin. The patient was a woman, aged twenty-seven, who had had diabetes for eleven years. Her diabetes was easily controlled with regular insulin, but when she was placed on protamine-zinc insulin, acidosis and severe glycosuria developed. On intradermal injection of protamine-zinc insulin there was a positive reaction, whereas regular insulin gave none. There were no masses beneath the skin at the site of injection. The authors expressed the opinion that an allergic reaction, as evidenced by the positive skin response, altered the protamine-zinc insulin and thereby prevented it from breaking down and liberating the insulin in the usual manner.

Beamer and Eadie[8] report that insulin fails to lower the blood sugar in most of their animals (rabbits) poisoned with diphtheria toxin. This resistance to insulin may be annulled by the injection of ergotoxin.

The following conditions have at times been as-

sociated with an increased requirement for insulin: destructive processes in the pancreas, with limitation of insulin-producing tissue, as in cancer, hemochromatosis, multiple calculi and acute pancreatitis; other endocrine disturbances, such as hyperthyroidism and pituitary and adrenal dysfunction; infection; disturbances of function of the liver, as in cirrhosis, chronic passive congestion, hemochromatosis and syphilis; disturbances of function of the skin and muscles, owing to complicating disease, poor development or disuse; cardiac complications with decompensation, edema and shock or circulatory collapse; diabetic acidosis and coma; and damage to the brain stem.

It must be emphasized that most of these disturbances have relatively little effect on the requirement for insulin. Occasionally some of them, such as hemochromatosis, have been associated with great resistance to insulin.

In the case that we have reported we were unable to find any definite reason for the large amounts of insulin required for control of the diabetes prior to operation. As stated, necropsy revealed abnormal-looking islands of Langerhans in the head of the pancreas, and hyalinization of the islands in the tail of the organ. This, however, is a common finding, not only in the pancreas of diabetic patients but in the pancreas of persons who die with no diabetes. It cannot explain the resistance to insulin. The liver, testes, pituitary body and suprarenal glands were normal on gross and microscopic examinations. Normal blood pressure and absence of signs of Cushing's syndrome tended to rule out dysfunction of the suprarenal glands. A small adenoma was present in the left lobe of the thyroid. There was, however, no evidence of hyperthyroidism clinically, and the basal metabolic rate was –9 and –3 per cent on two occasions. It is true that the patient had had intermittent distress in the right upper quadrant of the abdomen for about ten years, and that there was roentgenologic evidence of a non-functioning gall bladder. However, the sedimentation rate was only 7 mm. at the end of one hour, the white-cell count was only 5000, and there was no elevation in temperature. The wall of the gall bladder was thickened and slightly infiltrated. The evidence in favor of infection as the cause of the unusual requirement for insulin seems inconclusive; that present in the lungs was in the nature of a terminal development.

It is interesting to note that although the patient was excreting some sugar in the urine, it was only after he was placed on a low-carbohydrate, high-fat diet that the requirement for insulin began to rise steadily and continued to do so until the day he was operated on. That this may have contributed to the increased requirement is possible but improbable. All the diets used in the treatment of diabetes in the clinic were relatively low in carbohydrate until recently, yet this is only the second or third case among many thousands in which there has developed such a degree of insulin resistance.

Weakness caused by inadequate caloric intake — the patient was overly cautious and did not eat his full diet — resulted in curtailment of muscular activity. As Smith and Smith[9] have shown, exercise diminishes hyperglycemia following ingestion of food in normal subjects and in cases of controlled diabetes, but fails to do so in cases of uncontrolled diabetes. This decrease in amount of activity perhaps played a role in the increased insulin requirement in this case, but that it did so to any great extent is most unlikely, to judge from other experiences.

Harrop and Benedict[10] many years ago demonstrated that insulin retarded the excretion of potassium. At the time we were treating this patient, Kendall[11] reported the results of experiments on partially depancreatized rats. Following the ingestion of potassium chloride there was a marked increase in the amount of glucose excreted. This seemed to give support to his thesis that the amount of potassium retained in the body might influence the conversion of glycogen and protein to glucose. On the basis of his observation, we placed the patient on a diet containing only 1.2 to 2.0 gm. of potassium per day. The concentration of potassium in the serum fell from an abnormally high value of 31 mg. per 100 cc. to a normal value of 20 mg. on the ninth day of the diet, and the requirement for insulin fell in seven days from 260 to 180 units. However, the requirement then began to rise (Fig. 1).

In 1933, Barnes, Regan and Nelson[12] reported the amelioration of experimental diabetes in dogs following the prolonged injection of female sex hormone. This experiment was repeated later on monkeys by Nelson and Overholser.[13] On the basis of their observations, 10,000 units of dihydroxyestrin was injected daily for five days without effect. The requirement for insulin even rose for four days; however, no conclusions can be drawn from this, because the injections may not have been continued for a sufficiently long period.

The only conclusion justifiable from the report of this and other similar cases is that nothing is now known that will satisfactorily explain insulin resistance. Some antagonist to insulin that is not present when the treatment is begun must develop

in the course of continuous treatment, because at the beginning the patients do not show this resistance. However, the nature of the antagonist remains obscure. The condition seems to be analogous to the development of insensitivity to parathyroid hormone after it has been given for several weeks to patients with parathyroid tetany, although the latter is much more regular. Also possibly related is Collip's[14] observation of so-called "antibody formation" after long-continued administration of extracts of the anterior lobe of the pituitary body, notably with the thyrotropic hormone. The activity of the hormones of the parathyroid glands and anterior pituitary body apparently depends on the integrity of a basic unit the size of a molecule of protein, which therefore probably possesses antigenic properties. The same is true of insulin. The molecular weight of crystalline insulin as determined by Sjögren and Svedberg[15] is 35,100—almost identical with the values obtained for egg albumen and Bence-Jones protein. These investigators expressed the opinion that insulin is a well-defined protein and that the physiologic activity of the hormone is a property of the insulin molecule itself or of some special group within it. Insensitivity to hormones of simpler chemical structure, such as estrin and thyroxine, has not been reported. That encountered with hormones of the complexity of proteins may depend on antibody-like substances in the blood or, when circulating antibodies are not demonstrable, as in most of these cases, on a type of immunity reaction which, as has been suggested by the work of Gordon, Kleinberg and Charipper,[16] may be limited to fixed tissue cells, such as those of the reticuloendothelial system.

Summary

A case of insulin resistance is reported in which no definite cause for the resistance was found. Necropsy disclosed only terminal bronchopneumonia and recent abscesses of the right lung. Large amounts of sodium chloride were given, with only slight temporary improvement. The concentration of potassium in the serum was abnormally high; on a low-potassium diet it decreased to normal, and the requirement for insulin decreased temporarily. Administration of dihydroxyestrin did not seem to affect the requirement.

Conditions are mentioned that have at times been associated with diminished sensitivity to insulin. None of them were apparently involved in this case.

Nothing is now known that will satisfactorily explain insensitivity to insulin of the high degree encountered in cases like the one reported. Some antagonist that develops during the course of treatment is involved, and the suggestion is advanced that, owing to the protein nature of insulin, insensitivity to it may result from a type of immunity reaction limited to fixed-tissue cells, such as those of the reticuloendothelial system.

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THE TREATMENT OF LEUKEMIA BY RADIO-ACTIVE PHOSPHORUS*

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IN THE course of a series of experiments on the effect of radiation from temporarily radio-active phosphorus on cells and tissues, it became of interest to note this effect on some of the more sensitive human cells. The circulating leukocytes in human leukemia appeared to be the most suitable form to compare with the results obtained on certain animal tissues. Since a number of cases of leukemia had been treated with radio-active phosphorus from the Berkeley cyclotron by Lawrence and his associates,[1] this seemed to be a justifiable procedure. It has become well established, however, that satisfactory responses in chronic leukemias may be obtained, at least temporarily, by x-ray irradiation. Consequently, it was held inadvisable to subject such patients to a new and relatively untried type of radiant energy, and cases of acute or subacute leukemia were selected, since in them the established methods of radiation therapy leave much to be desired.

The radio-active phosphorus used in the treatment of these cases was chiefly obtained from the Harvard cyclotron.‡ At first, red phosphorus bombarded in the target chamber of the cyclotron was utilized. Later, in order to obtain a more concentrated source, phosphorus in the form of iron phosphide was placed on a probe within the deuteron stream of the cyclotron. A portion of the phosphorus was thus made radio-active. This phosphorus has a half-life of 14.5 days, and gives off a fairly penetrating beta radiation.

The phosphorus thus treated was changed by standard chemical methods to dibasic sodium phosphate. This was calibrated as to radio-activity on a modified Lauritsen-type electroscope.[2] An error of approximately 10 per cent in measurement of very small samples exists. It is, however, amazingly sensitive, particles of radio-active phosphorus as small as 3.5×10^{-14} mg. being detectible with its aid.

The desired amount of radio-active phosphorus, ranging from 1 to 4 millicurie equivalents, was dissolved in 5 per cent glucose and physiologic saline solution prepared for intravenous use, sterilized and injected intravenously into the patients. In all cases treated elsewhere the phosphorus had been given by mouth. Oral administration, however, has a disadvantage in that the proportion of phosphorus absorbed by way of the gastrointestinal tract is variable and frequently over 10 per cent may fail to be absorbed. On the basis of animal experiments,[3, 4] the injected phosphorus is shown to be absorbed selectively in the various organs and tissues. Fortunately, those in which the major deposit of leukemic cells occurs — the bones, the liver, the kidneys and the spleen — take up relatively large amounts.

In all the cases, the excretion of radio-active phosphorus was followed in the urine. That present in the feces, when the substance has been intravenously administered, is a relatively unimportant fraction. The concentration in the blood was checked from time to time in order that excessive doses should not be given. Large doses of radio-active phosphorus have been shown to produce marked fibrosis and aplasia of the hematopoietic tissues.[1]

The following are abstracts of the records of four cases of acute or subacute leukemia that have been treated.

CASE REPORTS

CASE 1. A 35-year-old man, referred by Dr. J. W. Norcross, of the Lahey Clinic, Boston, entered the Palmer Memorial Hospital on January 8, 1940, with a diagnosis of subacute myelogenous leukemia. The past history is particularly interesting in that the patient had been a professional blood donor for a number of years. Seven months previously he noticed weakness, and a diagnosis of myelogenous leukemia was made. He was given Fowler's solution and several transfusions. During several months x-ray treatment was given, without apparent general benefit, although the white-cell count was kept below 14,000 for some time. Numerous transfusions were given. He developed purpuric lesions of the skin. On admission the red-cell count was 3,500,000, with 0.5 per cent reticulocytes, the hemoglobin 62 per cent, the white-cell count 41,200 and the hematocrit reading 31 per cent. The differential count was 12 per cent polymorphonuclear leukocytes, 12 per cent band forms, with 9.5 per cent lymphocytes, 1 per cent basophils, 0.5 per cent abnormal monocytes, 4.5 per cent metamyelocytes, 6.0 per cent myelocytes, 4 per cent premyelocytes and 50.5 per cent blasts. The platelet count was 171,000.

On January 9 the patient received intravenously 750 cc. of 5 per cent glucose and physiologic saline containing 5.6 gm. of dibasic sodium phosphate, of which 2.6 millicurie equivalents of the phosphorus was radioactive. Frequent checks of the concentration of the blood and determina-

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tions of the rate of excretion were made. There was no reaction following the injection except for a slight sensation of fullness and a dull ache in the lower back, which passed off in about 3 hours. The white-cell count after 2 days had dropped to 33,000. On the 3rd day the count rose to 75,300, with approximately the same differential as on admission. At the patient's request a 500-cc. transfusion was given, to which he had a severe reaction. He recovered promptly and felt very well.

On January 16 an additional dose of irradiated phosphorus was given intravenously — 0.9 millicurie equivalent in 3.7 gm. of dibasic sodium phosphate dissolved in 500 cc. of 5 per cent glucose and physiologic saline solution. The following day the white-cell count was 27,300, and on January 19 it was 19,600. The differential count showed 6 per cent polymorphonuclears, 11.5 per cent band forms and 49 per cent blasts. On January 22 the white-cell count was 35,000, with a differential essentially similar to that given above.

The patient returned home, where he was considerably more active than he had been previously. The white-cell count on January 29 was 21,450. On January 31 and February 8 and 15 he received transfusions of 500 cc. On February 19 he was readmitted for further therapy; the white-cell count was 94,500 with 72 per cent blast forms. He showed several purpuric foci and a focus of swelling in the right calf. On February 20 he received intravenously 1.4 millicurie equivalents of radio-active phosphorus in 700 cc. of 5 per cent glucose and physiologic saline. The next day the white-cell count dropped to 61,000, and 1 millicurie equivalent of radio-active phosphorus was given intravenously. The patient was discharged on February 21, with a white-cell count of 97,500, to spend the holiday at home. While he was there his breathing became obstructed, presumably by hemorrhage into the cervical muscles, and he died before aid could be obtained. Permission for an autopsy was not obtained.

CASE 2. A 55-year-old man, referred by Dr. Richard H. Sweet, of Boston, was admitted March 28, 1940, with a diagnosis of acute lymphatic leukemia. He was referred from the Chelsea Memorial Hospital, which he had entered March 8 with a history of a cold 1 week before entry, chills, pain in the left chest and the coughing of bloody sputum. There was a left-upper-lobe pneumonia, and a Type 32 pneumococcus was recovered from the sputum. On physical examination at that time the spleen and lymph nodes were enlarged and the white-cell count was over 100,000, the cells being chiefly lymphocytes. On entry to the Palmer Memorial Hospital, hematologic studies showed an acute lymphatic leukemia. The patient stated that he had noted some lumps in his neck. Previous to his present illness his appetite had been good; he had had no weakness or palpitation, and had worked at loading coal into a coke oven.

On admission the red-cell count was 4,300,000, the hemoglobin 76 per cent and the white-cell count 118,500, with 10 per cent polymorphonuclear leukocytes, 89 per cent lymphocytes and 1 per cent large mononuclears. On April 3 the white-cell count was 118,000. Examination of a biopsied lymph node from the left axilla showed acute lymphatic leukemia. X-ray therapy was given to the left lower lung field because of partial atelectasis of the left lower lobe, assumed to be due to mediastinal pressure.

On April 12 the white-cell count was 20,500, with 8 per cent polymorphonuclear leukocytes, 90 per cent lymphocytes and 2 per cent large mononuclears. That day the patient was given intravenously 3 millicurie equivalents of radio-active phosphorus in 7.3 gm. of dibasic sodium phosphate in 500 cc. of 5 per cent glucose and saline solution. On April 25 the white-cell count was 7300, with 3 per cent polymorphonuclear leukocytes and 93 per cent lymphoid cells.

The patient's condition remained fairly satisfactory, with no complaint and no diminution in the swelling of the peripheral lymph nodes. On May 9 a bone-marrow biopsy was performed; the section showed a picture of acute lymphatic leukemia, with marked fragility of the lymphoblasts and small numbers of myeloid cells. A study of bone-marrow elements was made by Dr. Juan Picena. The results are shown and contrasted with earlier findings in Table 1.

TABLE 1. *Study of Biopsied Bone-Marrow Specimens from Case 2.*

TYPE OF CELL	INCIDENCE APRIL 8, 1940	INCIDENCE MAY 9, 1940
	%	%
Hemohistioblasts	0.5	0.0
Hemocytoblasts	33.5	21.0
Myeloblasts	0.5	0.5
Premyelocytes	0.5	1.0
Myelocytes	1.5	4.0
Metamyelocytes	3.0	5.5
Polymorphonuclear leukocytes	1.5	5.0
Proerythroblasts	0.0	0.0
Basophilic erythroblasts	0.5	0.5
Polychromatic erythroblasts	1.0	8.0
Orthochromic erythroblasts	2.5	14.0
Monoblasts	0.0	0.0
Monocytes	0.0	0.0
Lymphoblasts	0.5	0.0
Prolymphocytes	2.5	0.0
Lymphocytes	52.0	40.5
Rieder-Türck plasma cells	0.0	0.0

On May 11 the patient received 2.8 millicurie equivalents of radio-active phosphorus in 8 gm. of dibasic sodium phosphate. There was no reaction. He was discharged May 14 with a white-cell count of 7700; the polymorphonuclear leukocytes had increased to 52, and there were only 40 per cent lymphoid forms. The general condition continued good. On May 23 the weight was 132 pounds, a gain of 9 pounds since April 16.

On May 29 the patient was readmitted and 1.2 millicurie equivalent of radio-active phosphorus in 2.9 gm. of dibasic sodium phosphate in 500 cc. of 5 per cent glucose and saline solution was given intravenously, without reaction. The red-cell count was 3,010,000 and the white-cell count 7500, with 44 per cent polymorphonuclear leukocytes. The patient was discharged on May 31.

On June 13 the patient appeared to be in satisfactory condition with no complaint, and there appeared to be slightly less swelling of the peripheral lymph nodes. On June 27 the condition was the same, and the white-cell count was 6400.

On August 6 the patient was readmitted for complete study. His condition was still good. The peripheral lymph nodes were approximately the same size as previously. The white-cell count was 6300, with 23 per cent polymorphonuclear leukocytes, in contrast with 118,500 and 10 per cent respectively on the first admission. It was intended to give him 2 millicurie equivalents of radio-active phosphorus, but owing to a reaction, with nausea and shortness of breath, the injection was discontinued after 0.6 millicurie equivalent had been given. The patient was discharged in satisfactory condition, and has continued active and without pain, although not strong enough to do heavy work.

On September 26 he received 1.5 millicurie equivalents of radio-active phosphorus intravenously, and was discharged with a white-cell count of 8450, of which 48 per cent were polymorphonuclear leukocytes. On October 17 he was moderately active, and his condition fair, with a red-cell count of 2,300,000 and a white-cell count of 8050 with 46 per cent polymorphonuclear leukocytes.

Case 3. A 68-year-old man, referred by Dr. Howard F. Root, of Boston, was admitted April 11, 1940, with a diagnosis of acute lymphatic leukemia. For the previous few months he had been slightly short of breath and for 4 months had had some orthopnea. For 2 months he had noted swelling of the ankles in the daytime. On admission the red-cell count was 1,760,000, the hemoglobin 34 per cent and the white-cell count 42,550, with 19 per cent polymorphonuclear leukocytes, 75 per cent lymphoid cells, 4 per cent large mononuclears and 2 per cent eosinophils. The peripheral lymph nodes, liver and spleen were moderately enlarged.

On April 17 the patient received a transfusion of 500 cc. of citrated blood. On April 18 he received intravenously 2.1 millicurie equivalents of radio-active phosphorus in 11 gm. of dibasic sodium phosphate in 800 cc. of 5 per cent glucose and saline solution. The following day the white-cell count was 37,500. The results of sternal marrow biopsies April 22, June 6 and July 11 are shown in Table 2.

Table 2. *Study of Biopsied Bone-Marrow Specimens from Case 3.*

Type of Cell	Incidence		
	April 22, 1940	June 6, 1940	July 11, 1940
	%	%	%
Hemohistioblasts	0.0	0.3	0.0
Hemocytoblasts	0.5	1.3	3.8
Myeloblasts	0.0	0.4	0.3
Premyelocytes	0.0	0.4	0.0
Myelocytes	0.5	0.8	0.6
Metamyelocytes	0.3	1.7	0.7
Polymorphonuclear leukocytes	0.9	3.3	1.4
Proerythroblasts	0.0	0.1	0.0
Basophilic erythroblasts	0.0	0.4	0.4
Polychromatic erythroblasts	0.5	1.3	1.1
Orthochromic erythroblasts	0.5	0.8	0.0
Lymphoblasts	3.3	2.5	4.0
Prolymphocytes	4.5	3.6	10.2
Lymphocytes	89.0	83.9	80.9
Rieder-Türck plasma cells	0.0	0.6	0.4
Monocytes	0.0	0.1	0.0

The patient was discharged improved April 23. He was active at home, and returned to the hospital May 8 on request. On May 11 the red-cell count was 2,340,000, the hemoglobin 50 per cent and the white-cell count 19,850, with 27 per cent polymorphonuclear leukocytes and 59 per cent lymphoid forms. He then received intravenously 0.8 millicurie equivalent of radio-active phosphorus in 550 cc. of 5 per cent glucose and saline solution. He was discharged May 15 with a white-cell count of 17,200.

On June 3 the patient re-entered the hospital and received intravenously 3.9 millicurie equivalents in 15.5 gm. of dibasic sodium phosphate in 500 cc. of 5 per cent glucose, without reaction. On June 5 the white-cell count was 11,600. On June 6 the patient received a transfusion of 500 cc. and was discharged.

On July 10 he re-entered, still feeling well. The red-cell count was 2,570,000 and the white-cell count 11,200, with 23 per cent polymorphonuclear leukocytes. The patient received intravenously 3.8 millicurie equivalents of radio-active phosphorus in 1 gm. of dibasic sodium phosphate in 800 cc. of 5 per cent glucose and saline solution, without reaction. On July 15 he was given a 500-cc. transfusion, followed by febrile reaction. He was discharged temporarily improved July 16.

On September 25 he received 2.5 millicurie equivalents of radio-active phosphorus intravenously and was discharged with a white-cell count of 11,350, of which 57 per cent were polymorphonuclear leukocytes. On October 17 his condition was as before and he was working steadily; the red-cell count was 3,450,000, and the white-cell count 9750 with 50 per cent polymorphonuclear leukocytes.

Case 4. A 57-year-old man, referred by Dr. Richard L. V. Wingate, of Cambridge, was admitted June 26, 1940, with a diagnosis of subacute lymphatic leukemia. The red-cell count was 3,450,000, the hemoglobin 65 per cent and the white-cell count 126,500. All the white cells were of the lymphoid series. The platelets were decreased. In various portions of the body dull-red, firm swellings had appeared, which ran a sluggish course, eventually drained necrotic material, and left a clean-walled cavity which healed with the formation of a small scar. Practically all the lymph nodes were enlarged in varying degrees, the largest, in the right axilla, being 7 cm. in diameter. The spleen was palpable 3 cm. below the costal margin and the liver was palpable just below the costal margin.

On June 28 the patient received intravenously 4 millicurie equivalents of radio-active phosphorus in 0.8 gm. of dibasic sodium phosphate in 500 cc. of 5 per cent glucose in physiologic saline solution. There was no reaction. The general condition seemed fairly satisfactory. The white-cell count on the following day was 124,500, still with 100 per cent lymphoid cells. The patient was discharged June 30 and was readmitted July 9 having done fairly well since his last visit. The white-cell count was 77,750, the cells still being entirely of the lymphoid series. He had developed a brawny, red induration involving the lower ends of the right internal thigh muscles. This was somewhat painful and similar to the infiltration which he had earlier had elsewhere. On July 11 an aspiration biopsy of the sternum was done, which showed 1.8 per cent cells of the granulocytic series, 1.4 per cent of the erythrocytic, 2.8 per cent hemocytoblasts and the remainder lymphoid cells. The same day the patient received 1 millicurie equivalent of radio-active phosphorus, without reaction. Following this there was decided regression of the indurated region of the right thigh.

The patient was discharged July 12. He was to have returned to the Out Patient Department on August 8, but by that date he had had continued difficulty with the lesion in his right thigh. This had increased in size and had become markedly tender, finally discharging approximately 120 cc. of thin, slightly hemorrhagic fluid. The remaining defect was clean, and closed in with apparently normal granulation tissue. On August 15 the general condition was less satisfactory, and death occurred in late September.

As has been pointed out by Lawrence,[8] the doses of radio-active phosphorus have been marked out empirically, and probably are not optimal. The intravenous method of administration, which we have used, seems most suitable. Careful study of the concentration of radio-active material in the blood and the rate of its excretion is important.

SUMMARY

Four cases of acute or subacute leukemia were treated with temporarily radio-active phosphorus prepared on the Harvard cyclotron and injected intravenously in the form of dibasic sodium phosphate. The doses ranged from 1 to 4 millicurie equivalents. Some improvement has been seen in two patients as evidenced by their general condition, level of white-cell count and condition of bone-marrow. These patients are moderately active. Two patients showed no significant response beyond minor changes in white-cell count; both are dead. This therapy is experimental, and does not displace present methods of radiation for the treatment of leukemia.

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NOTES ON THE HISTORY OF RHEUMATISM AND GOUT*

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CHRONIC arthritis is probably the oldest disease of which we have definite evidence. Pemberton and Osgood[1] have collected examples of the disease from reports of fossils dating back in remote antiquity six hundred million years. The dinosaurs of a hundred million years ago can be imagined limping through the lush growth on their way to tumble into immortality in the ponds and slime. The earliest forebears of our cattle and horses, in the Eocene Period, the crocodile lying under an Egyptian sun fifteen million years ago and the camel of the Pliocene Era have left us their arthritic bones. The cave bear and the saber-toothed cat, of the Pleistocene Era, five hundred thousand years ago, died sufferers from spondylitis deformans. The Neolithic Man of seventy-five thousand years ago wielded his club with fingers as gnarled and stiffened as those we observe among our elders, while his weaker son had a "poker spine."

Egypt's sands have yielded remains of arthritic limbs. Smith and Jones[2] studied over ten thousand bodies from the Nile Valley, which ranged in time over a period of seven thousand years, from the prehistoric Nubians down through the Empire Period to the early Christian Copts. They found many cases of spondylitis deformans and even more cases of apparent osteoarthritis. None of these cases developed before the epiphyses had closed, and the authors do not report the finding of rheumatoid arthritis. They record only 1 case of true gout, and the patient was not a native Egyptian, but a Christian immigrant, probably from Syria.[3] Sir Marc Armand Ruffer,[4] however, has described lesions in Egyptian mummies compatible with those of rheumatoid arthritis as well as of osteoarthritis.

Hippocrates did not clearly differentiate the types of arthritic disease. In the *Prorrhetics*[5] he remarks, "Of affections of the joints, the most dangerous are those seated in the thumb and great toe." And, he pronounces as incurable the occurrence of joint disease in persons "who are aged, have tofi in their joints, who have led a hard life and whose bowels are constipated," unless they have "an attack of dysentery, or other determination to the bowels."

In the *Aphorisms*,[6, 7] there are eighteen that refer to disease of the joints. He may have seen what is referred to today as menopausal arthritis, for he says: "A woman does not take the gout, unless her menses be stopped."[7] The statement, "A young man does not take the gout until he indulges in coition,"[7] might possibly have been a reference to the arthritis of a Neisserian infection. Hippocrates seems to have observed a connection between the sexual life and joint disease, as in the two aphorisms just quoted and also in his remark, "Eunuchs do not take the gout nor become bald."[7]

From this brief review it would seem that although Hippocrates saw many of the clinical types of arthritis, he made little attempt at classification. It is of general interest that he mentioned venesection, a practice which for centuries was the physician's first thought in therapy, and the origins of which seem lost in antiquity.[8]

The first century after Christ produced three im-

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portant and accessible writers, Celsus and Galen at Rome, and Aretaeus in Byzantium. Celsus[9] draws largely from Hippocrates, as when he remarks: "Joint disorders, too, such as foot and hand aches, if they attack young people and have not induced callosities, can be resolved; for the most part they are removed by dysenteries and fluid motions, whatever the sort."[10] He also restates Hippocratic remarks on the menopause and on coition,[7, 11] on the occurrence of pain in spring and fall[6, 12] and on the subsidence of pain within forty days.[6, 13] Celsus does not attempt to classify the arthritides. He discussed rheumatic fever unknowingly when he wrote: "Children in whom there has been nose-bleeding, which then has ceased, are sure to be troubled by pains in the head, or they get some severe joint ulcerations, or they also become debilitated by disease."[14]

Galen applied the theory of humoral pathology to arthritis, and seems to have distinguished gout as a separate entity, a new form of podagra that was inheritable and related to luxurious eating and drinking.[15]

Aretaeus gives a good account of the clinical picture of what resembles rheumatoid arthritis, describing the onset in small joints, the spread through the body, systemic changes and deformities. He, also, must have referred to rheumatic fever when he wrote, "In many cases, the gout has passed into dropsy and sometimes into asthma, and from this succession there is no escape."[16]

In the Byzantine Empire during the sixth and seventh centuries lived two of the later Greek compilers, Alexander of Tralles and Paul of Aegina. They drew from both Greece and Rome. Their writings summarize the system of medicine which developed from the Greek theory of humoral pathology.*

Alexander of Tralles lists the following causes of "podagre": effusions of hot blood into the joint cavity, defluxions of bile, of black bile, of phlegm, and alterations of the simple quality of the humors.[18] His clinical types do not correspond to our clinical entities, but they served him as the basis for an extensive therapeutic scheme.

Paul of Aegina considered the disease to be due to "a preternatural humor and a weakness of the parts meeting together. . . . The prevailing humor is sometimes bilious, sometimes sanguineous, sometimes melancholic, but for the most part it is pituitous and crude, being engendered by excess of food, indigestion and want of exercise."[19] He gives a complete list of "precursory causes" that includes a good deal that is applicable today. Even now little can be added to what he said about etiology: "And some from accidents, as a blow, a sprain or the like, experienced the first attack of this complaint, the materials of the disease having previously lain quiet in the system until roused by the proximate cause."[19] "Sorrow, care and other passions of the mind" are on his list.

The joint of bilious humor, according to Paul,[20] was pale, red, hot and acutely painful without much swelling. That of the melancholic humor was characterized by a dark skin. That of the pituitous humor had a white and watery skin, with the pain and swelling lying latent and developing slowly. The joint in the grip of the sanguineous humor had a sanguineous color.

The Arabian, Avicenna, 980–1036, was a famous and skilled physician, whose *Canon of Medicine*[21] was a leading medical text. He mentions "gout" attacks, pain in the joints, sciatica, pain in the back and hips, and in Book III, as yet untranslated, he devotes a section to the special pathology of muscles, joints and feet.

The term "gout" is derived from the Latin *gutta*. Alexander of Tralles[22] is said to have used it in the sixth century in the sense of arthritic disease. Radulfe[23] in the thirteenth century again used the word. Ballonius (Guillaume de Baillou),[24] a graduate of the University of Paris in 1570, first used the word "rheumatism" as a name for acute arthritis. *Gutta* in its original meaning stood for droppings from the nose. "Rheum" likewise means a watery or catarrhal discharge, and is derived from the Greek ῥέω, "to flow." Both terms are derived from words with the same fundamental meaning; their application to arthritis came about through the humoral theory of this disease.

From the seventeenth century onward come the descriptions of specific arthritic conditions. Richard Wiseman,[25] King Charles II's surgeon general, in 1672 described a specific entity, "tumor albus," that we now recognize as tuberculosis of the joints.

Thomas Sydenham,[26] 1624–1689, is responsible for clearly separating gout from acute and chronic arthritis. He[27] wrote a vivid account of the gout, the more vivid since he himself was a sufferer from the disease and died from the effects of nephrolithiasis. He wrote, in *Of a Rheumatism;*

> When this Disease is not accompany'd with a Fever, it is often taken for the Gout, tho it differs essentially from that, as plainly appears to any one that well con-

*Plato and Aristotle taught that there were four qualities — hot, cold, moist and dry — and four bodily humors — blood, bile, black bile and phlegm. Health was the equipoise of the humors, disease the imbalance. Drugs were classified in systems, according to the qualities they contained. Therapy was based on the Hippocratic teaching that "diseases are cured by their contraries."[17]

siders both diseases. . . . It is frequent enough now, and though it seldom kills anyone when the Fever is off, yet upon the account of the Violence of the Pain, and the Continuance of it, it is not contemptible.[28]

Sydenham also clearly distinguished between the acute and chronic forms of arthritis. He spoke of the chronicity of arthritis, of remissions and exacerbations, of flexion deformities and ankylosis. He introduced the term "scorbutical rheumatism," but it is not clear whether this is intended to cover cases of arthritis associated with clinical scurvy, or is a catchall to hold cases that had the features of both gout and chronic rheumatism.[29]

Boerhaave,[30] who lived in Leyden in the early eighteenth century, taught that there were two diseases, gout and rheumatism. The latter probably included without differentiation all our modern types of arthritis deformans.

Cullen's *Methodical System of Nosology*,[31] divides all disease into fevers, neuroses, cachexias and local disorders. Among the fevers Cullen lists the arthritic diseases in the following groups: rheumatism, arthrodynia ("the consequence of the rheumatism"), odontalgia, podagra (gout) and arthropuosis.[31]

Heberden,[32] in 1782, described the arthritic nodes which go by his name, but his successor, Haygarth, first associated these nodes with a disease entity. To quote from his *Clinical History of the Nodosities of the Joints*:

> There is one painful and troublesome disease of the joints of a peculiar nature, and clearly distinguished from all others by symptoms manifestly different from the Gout, and from Acute and Chronick Rheumatism.[33] . . . This disease has hitherto passed under the name of Gout or Rheumatism, or perhaps has been most commonly called Rheumatick Gout. . . . I have ventured to call it the Nodosity of the Joints.[34]

Haygarth also described, in 170 of the 10,459 patients on whom he kept careful clinical records, a disease called "acute rheumatism or rheumatic fever." He lacked by two decades the advantages of the stethoscope and therefore did not recognize heart disease in his patient who died: "On the tenth Day . . . the swelling of the Hands receded; her breath became shorter, with cough and spitting of blood which soon terminated fatally. . . . The Rheumatick inflammation seems here to have been translated from the joints to the lungs."[35]

Scudamore's classic *Treatise on the Nature and Cure of Rheumatism* first appeared in 1817. It is noteworthy for an excellent survey of ancient and contemporary literature, and for its proposition that rheumatism was "pain of a peculiar kind, usually attended with inflammatory action, affecting the white fibrous textures belonging to muscles and joints. . . ."[36] His classification included gout and rheumatism — acute, subacute and chronic.

During Scudamore's lifetime came the realization that heart disease was regularly associated with rheumatic fever. The 1827 edition of his treatise contains an extensive review of the early literature on this subject. He wrote, "There is not, probably, a more dangerous form of disease, than a sudden seizure of the heart during the inflammatory state of the system in acute rheumatism."[37] According to Scudamore, Dr. David Pitcairn, at St. Bartholomew's Hospital, taught as early as 1788 that "persons subject to rheumatism, were attacked more frequently than others, with symptoms of an organic disease of the heart . . . and . . . called the latter disease 'Rheumatism of the Heart.'"[38] This statement is said to have first appeared "in the second edition of Dr. Baillie's *Morbid Anatomy*, which was published in 1797,"[39] and was taken by Scudamore from a paper by Dr. J. C. Wells, "On Rheumatism of the Heart,"[40] in the *Edinburgh Medical Journal* for 1806 a review of Dr. Odier's *Manuel de médecine pratique* stated that Odier wrote of rheumatic affection of the heart.[39] A paper by Sir David Dundas, in the first volume of *Medical and Chirurgical Transactions*, described 9 cases of rheumatic disease of the heart, of which 6 were examined post mortem.* Thus by 1812 rheumatic heart disease was definitely known.

However, in these accounts there are no descriptions of valvular disease or of endocardial involvement; they describe the symptoms of palpitation, breathlessness and anasarca, and the pathology of cardiac enlargement and pericarditis. It was not until after the invention of the stethoscope in 1819 that the valvular involvement could be described during life.

Thus Bouillaud is generally credited with the first description of rheumatic heart disease. In 1832–1833 he described cases of endocarditis and pericarditis associated with acute rheumatism. His famous Law of Coincidence established the occurrence of heart disease both concomitantly with and as a sequel to acute articular rheumatism.[42] He noticed and described cardiac enlargement, change in the shape of the chest, "a bellows, file or saw sound," irregularities in the pulse and "different abnormal sounds, some arising from the rubbing of the opposite coats of the pericardium against each other, others from the

*These cases are discussed at length in a footnote in Scudamore.[41] Of Dundas's conclusion, Scudamore then (1817) stated, "I should rather be disposed to consider the general rheumatism of the constitution to be a predisposing cause of this disease of the heart rather than to pronounce it rheumatism of this organ."

complication of pericarditis with valvular endocarditis."[43] However, he was far from the truth when he wrote:

> People long ago talked vaguely of gout flying to the heart, of rheumatism translated to the heart, &c &c. But as the nature of these gouty and rheumatic metastases had never been determined, they were considered to be accidents and not very common occurrences. A little later, in speaking of rheumatic metastases, observers placed, it is true, pericarditis among the number of accidents which these metastases were capable of producing, but they spoke of it slightingly or incidentally.[44]

It is but a relatively short time from 1833 to the present. The recent history of the problem of classification of arthritic disease is complicated, but has been well covered by several authors.[1, 23, 45]

I propose to return to the ancient world to review old methods of therapy. Hippocrates' methods of therapy are quite conservative. He mentions diet, regimen, baths, warm climate, purging and local applications. He does not lay down a schedule of rules for the treatment of arthritis.

Celsus is rich in methods of treatment. He[11] advised hot fomentations to the joints, hot plasters or cataplasms, and emollients as external applications. He recommended cupping and burning the skin with cauteries "to set up issues." These ulcers were to be kept open and massage was to be used, "in order that the materials of the disease, which have been doing harm by collecting, may be the more readily dispersed." He mentions bloodletting and the use of diuretics and clysters. He shows the Hippocratic influence in advising the patient to refrain "from wine, mead and venery for a whole year," and to use a regime of mild exercise, sweating, local application of oil, diuretics, purging and a diet "of the middle class."[12]

For severe pain Celsus recommends an ointment made of rind of poppy heads, boiled in oil and mixed with wax salve made of rose oil. One form of treatment that he mentions is of extraordinary interest. "The stone, too (which corrodes flesh), which the Greeks call sarcophagos, is carved out so as to admit the feet; when these are painful, they are inserted and held there, and are usually relieved."[13] No other reference to immobilization was found until some thirty years ago, when orthopedic surgeons began to use plaster-of-Paris casts for the immobilization of arthritic joints.

It is in Aretaeus that we first find reference to internal medication for which claims to specificity are made. Thus he wrote: "In gouty cases hellebore is the great remedy."[46] Hellebore contains veratrine, the only modern use of which is as a cardiac depressant, but its action in Greek medicine was probably as a desired purgative and for diuretic action. Aretaeus includes a significantly long list of common herbs useful for cataplasms, among which are "bread with the cooling parts of gourd and pompion, and simple cucumber, and the herb plantain and rose leaves."[46] Other common plants used by him are root of comfrey, herb cinquefoil, horehound with narrow leaves, parts of the citrous fruit not good to eat, dried figs and barley meal. We can see the pharmacopeia in its evolutionary process in such lists as these. One method of treatment he advised is "Let a goat feed on the herb iris, and when it is filled therewith, having waited until the food it has taken be digested in the stomach, let the goat be slaughtered, and bury the feet in faeces within the belly."[46]

Aretaeus has faith in his ability to cure early cases, but not well-established ones. He describes the usual course of a case of arthritis:

> Pain seizes the great toe; then the forepart of the heel on which we lean; next it comes into the hollow of the foot, but the ankle swells last; and they blame a wrong cause; some, the friction of a new shoe; others, a long walk; another again, a stroke or being trod upon; . . . On this account the disease gets to an incurable state, because at the commencement, when it is feeble, the physician is not at hand to contend with it; but if it has acquired strength from time, all treatment is useless.[47]

Alexander of Tralles[48] mentions the drug hermodactylus, or colchicum. He states that this will at once relieve arthritic pain, if given internally with pepper, anise, ginger, aloes and scammony. Colchicum has a remarkable history. Paul of Aegina in the seventh century states:

> Some, in the paroxysms of all arthritic diseases, have recourse to purging with hermodactylus; but it is to be remarked that hermodactylus is bad for the stomach, producing nausea and anorexia, and ought, therefore, to be used only in the case of those who are pressed by urgent business; for it removes rheumatism speedily, and after two days at most, so that they are enabled to resume their accustomed employment.[49]

According to Francis Adams,[50] Avicenna and Rhazes used colchicum, and Lanfrancus, "an early modern writer," mentioned it. However, because of its toxicity, somewhere the drug was condemned, and it was not used by Sydenham. It was rediscovered by Stoerck in Vienna in 1763, and soon took its proper place in medicine.[51]

Alexander had a different regime for each of his four types of arthritic complaint, based on the humoral qualities he believed to cause the disease.[52] For the bilious type there was a careful diet containing nothing bile-forming, a regime of moderate exercise, baths and an elaborate list of local

applications. The phlegmatic joint was injured by refrigerants, helped by calefacients; he approved blistering with cantharides, but not burning with iscae, which were local applications of flax and oil, set afire over the joint.[53] This practice of burning flax was mentioned in Hippocrates[54] and had its counterpart in Chinese and Indian medicine, where the burned substance was a moss, *moxa*.[55] Moxae were reintroduced during the seventeenth century; we find in Sydenham's writings a criticism of their use.[56] For the sanguineous type, bloodletting was indicated, including evacuation of blood from the joint space,[57] and articles of diet engendering blood were proscribed. Alexander's blood-builders were flesh, pork and sweet wine. For tophi, he recommended litharge, old oil, Dragon's blood, niter, turpentine and ammonia as local applications.[58]

Paul of Aegina had very similar methods. For the bilious humor he used purgative medicines "such as that from rhodomel, that from quinces, the antidote called picra and aloetic pills."[59] While the pain was acute he advised local applications, paregoric substances and narcotics. He recommended hermodactylus, purging and bloodletting for the sanguineous variety.[49] For the pituitous type he had what is practically a list of garden herbs — cabbage, parsley, vervain and fleabane — as local applications. A cataplasm of ox or goat's dung, honey, boiled barley meal, in oxycrate, was among his more picturesque remedies.[49]

For tophi, Paul advises the use of these mixtures:

> This is an excellent application for tophi in the joints: very old and acrid cheese pounded and applied with a decoction of fat swines' flesh, it also being old. . . .[60] The composition from dragon's blood is of wonderful efficacy for chalkstones and many other complaints, but is difficult to procure.[60]

The ancient equivalent of our steam bath is described thus:

> Some, for the entire removal of the complaint, boil whole wolves in oil, wherewith they cure arthritic cases; . . . And in like manner they boil hyaenas, making a discutient oil from them; and then filling the cistern of the bath with it, and putting the arthritic patients into it. . . .[60]

Avicenna, four centuries later, recommended baths of hot oil, more beneficial "if the flesh of the jackal or hyaena is boiled in it."[21] He also advised evacuant measures against the gout.[21] He used desiccants on the skin for a swollen joint, "as one does in the case of those afflicted with dropsy."[21]

The familiar propensity of the Arabians to use psychotherapy is illustrated by two tales from an Arabic collection of stories of the great physicians, called *Four Discourses,* which dates from about 1155 A.D. and is from the pen of the court physician of Samarkand.[61] In the first, Rhazes was called to attend the great lord, Amir Mansur, in Transoxiania, who suffered from rheumatism. After exhausting all his skill, Rhazes said to him, "Tomorrow I will try a new treatment, but it will cost you the best horse and mule in your stables." The next day Rhazes gave the amir douches of hot water and a draught which he had prepared, until the humors of his joints were matured. Then Rhazes took a knife into his hand, and stood for a while reviling the amir, telling him he was about to destroy him. The amir was furious, and partly from rage and partly from fear sprang to his feet. Rhazes immediately fled the country on the steeds that the amir had given him. Once safe across the Oxus, Rhazes wrote to the amir, explaining how his psychotherapeusis had worked to increase the natural caloric, which thus gained sufficient strength to dissolve the already softened humors. He closed by saying that it was inexpedient that they should meet again.

The second story is told of an unnamed court physician who was taken to treat a woman of the King's household for stiffness of the joints. He had recourse to psychic treatment: by first removing the woman's veil and then her skirt he called to his aid the emotion of shame, whereby a flush of heat was produced within her which dissolved the rheumatic humor.

From the Arabians it was five hundred years to Sydenham,[27] but in essentials the therapy of arthritis had not changed. Yet in one important respect Sydenham was far ahead of his time. He conceived of arthritic disease and gout as chronic diseases, and recommended a conservative regime. The patient should go to bed early and rise early, should keep the mind easy, should exercise regularly and should abstain from coition. He should refuse wine, and should substitute for it a "Dietetick Drink." This was a concoction of sarsaparilla, sassafras wood, china root, licorice root, anise seed and water. Of this he said, "Tho' the constant taking of them may cause some loathing for a week or two, they will afterward be as pleasing, and as acceptable, as any other liquors, to which he has been most accustomed."

Sydenham has a great deal to say against wine:

> For tho' it may supposed to do Good, by helping the Concoctions, the Disorders whereof I have long accounted the antecedent Cause of the Gout; yet, with respect to the containing Cause, it must be reckoned wholly injurious, for that it fires and exagitates the Humors, the Fomes of the disease, already prepared to give Battle. . . . Therefore those that are subject to the Gout, must take care that they use those Liquors that can neither cause Drunkenness when they are

> taken in a large Quantity, nor injure the Stomach, by chilling it. . . . I count Water, by itself, crude and injurious; and I have found it so to my Hurt: but Water may be safely drunk by young People.

For the treatment of the acute attack he recommended laudanum, mild purging and sweating. He does not mention colchicum, and conservatively he disapproves of much bloodletting.

Sydenham's treatment of acute arthritis was quite different.[62] This included the customary bleeding, a sweet tasting julep "to be drunk at leisure," local applications of cold to the joints and "glisters" of sugar and milk or sugar and violet water. He insisted that the patient be out of bed for part of the day, "for keeping bed constantly promotes and augments the Disease."[29]

He made use of electuaries, and in his treatise printed the formulas of two, a stomachic and an antiscorbutic. The latter included the "peels of six oranges" but no other citrous fruit.[63] The digestive electuary was a compound of the dried powders of thirty herbs, "gathered when they have most Virtue in them," dried in paper bags, and mixed with purified honey and canary wine.[27]

In the year 1805, when Haygarth wrote his *Clinical History,* his treatment of gout and arthritis had a modern tone. The following remedies were found useful: guaiacum, cinchona, leeches, "Warm Bathing and Pumping at Bath . . . at Buxton," vapor baths, sea baths, antimony, mezereum,* aconite, and the external use of oil and camphor and "bootikins."[64] For rheumatic fever he used bleeding, antimony, sudorifics, saline medicines, warm baths and Peruvian bark.†[65]

In the work of Bouillaud we have seen the stethoscope in action. It is strange that this man, who was so modern in his method of investigation, should be the worst bloodletter of whom we read. For the treatment of acute rheumatic fever he recommended bleeding four or five bowls the first day, then three bowls each the second and third days, followed by later bleeding by leeching, and venesection if the patient relapsed. He claimed to have treated 184 cases of acute rheumatic fever by this method, and said, "All of them have been cured except one."[66] He complained:

> Truly we know not why so many daily say that they bleed the same as we do, and that nevertheless they do not obtain the results which we announce. No, emphatically no; they do not bleed according to our method, whatever may be said to the contrary.[67]

*The dried bark of *Daphne mezereum,* containing a glucoside, daphnin.

†The Peruvian bark had been brought to Europe from South America in 1620 by the Spanish. Its quinine was to prove a great addition to the physician's armamentarium. Sydenham in 1670 already had recommended it as the best simple for arthritis. Haygarth lists his clinical results with Peruvian bark complete with case summaries in the most approved modern manner.

Bouillaud wrote these words in 1832. The stethoscope had been introduced, and had recently been given by vote the approval of the Boylston Medical Society of Harvard Medical School as an instrument likely to become useful in the clinic. Virchow was then a schoolboy who was to study fossils in the caves of the Pyrenees and introduce the term "arthritis deformans." The work of Charcot in France, of Robert Adams and Garrod in England, and of Goldthwait, Nichols and Richardson and others of their notable group in Boston, and Pemberton in Philadelphia, plunged the notions of arthritic classification into a welter of confusion, but eventually clarified and simplified the picture and led to the present workable classification. Medieval methods of bleeding, purging, puking and cupping were to give way before a therapy based on clinical and laboratory investigation of etiologic factors. The investigation is still going on, and our knowledge of specific causes is still incomplete. The nature, etiology and specific therapy of arthritis deformans remain among our most alluring medical problems, pre-eminent in medical, social and economic importance.

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CARCINOMA OF THE BREAST IN A TEN-YEAR-OLD GIRL*

Report of a Case

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IN THE last three decades only two well-authenticated cases of breast cancer before puberty have been reported,[1, 2] one in a girl of eleven, the other in a girl of twelve.

Deaver and McFarland[3] quote Thompson's authenticated case (1908) of adenocarcinoma of the left breast in an eleven-year-old girl. Although its existence had been known for a period of three years, the growth had not increased in size until shortly before admission to the hospital.

The occurrence of carcinoma of the breast in the decade following puberty is extremely, though less, rare. Lee,[4] in his study of 303 cases of breast cancer, found that the 2 youngest cases were both women of twenty-two. Hall and Bagby,[5] in reviewing 134 patients under the age of thirty-one with all types of carcinoma, found 22 proved cases of breast cancer; of these the 2 youngest were twenty-two. Krauss and Kline,[6] in their review of the literature in 1926, found 12 cases of confirmed unilateral carcinoma of the breast in patients under twenty-two.

CASE REPORT

A 10-year-old white, American-Irish schoolgirl (No. 44685) entered the Out-Patient Department of the Beth Israel Hospital on December 14, 1938, because of a lump in the right breast. Six years previously her mother had noted the lump. The child said she had hit her right chest on a car door that day. The mother believed that it might have grown during the previous year. There was no history of pain or tenderness. The patient had had measles, whooping cough and mumps before the age of 5. She was a normal, happy child. The mother was well. The father had died of pneumonia at 41.

Physical examination revealed a nodule 3 by 2½ by 2½ cm. under the right nipple. It was hard, irregular, sharply circumscribed, nontender and adherent to the overlying nipple, which was flattened. The mass was freely movable posteriorly. There were no lymph nodes in the axilla or supraclavicular region. X-ray examination of the tumor showed no evidence of calcification; that of the long bones, skull and chest showed no evidence of metastasis. The urinalysis was not remarkable. The red-cell count was 4,180,000, the hemoglobin 77 per cent (Sahli) and the white-cell count 10,000. The differential count was not unusual. Blood Hinton and Kahn tests were negative.

On December 16 the breast tumor and pectoral fascia were excised. A curved incision was made along the lower aspect of the tumor, which was exposed and found to be resting on the pectoral fascia. It had clear-cut borders on all surfaces except in its relation to the skin, to which it was firmly adherent. The tumor itself was firm and smooth. It was dissected from the overlying skin with difficulty and submitted for immediate frozen section. When the pathologist reported the presence of carcinoma, a wide skin area was excised, also the fascia overlying the pectoralis major. The border of the pectoralis was explored, and no lymph nodes were felt. One finger was introduced into the axilla, where no nodes were palpated. The wound was closed without drainage. The patient was discharged 8 days after the operation to the Tumor

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Clinic for follow-up. At the end of a year there was no evidence of recurrence.

The pathologist's report was as follows:

The specimen consists of a globular mass 2 cm. in diameter. The external surface is pink-gray, smooth and dull. Attached to it are several small lobules of pink-yellow fat. The consistence is uniformly somewhat firm. On cross-section the specimen cuts with a gritty sensation. Most of the cut surface is glistening and gray, with one small irregular, tan-yellow area. The point of a dull instrument applied to the cut surface causes no pitting. On squeezing and scraping the cut surface, a small amount of fluid is obtained. Immediate frozen section reveals carcinoma.

Microscopic section shows the tumor to be fairly well-demarcated from the surrounding thin rim of breast tissue. In most areas there is an encapsulating layer of concentrically laminated fibrous tissue about the

FIGURE 1.

tumor. This layer is contiguous with the fibrous-tissue septums of the breast. In no place is the encapsulating layer very thick; in many places it is extremely thin, and in a few spots the enclosed neoplastic epithelial cells are invading the thin encapsulating fibrous tissue (Fig. 1).

There is considerable variation throughout the tumor in the proportion of fibrous tissue stroma to carcinomatous tissue. In only a few fields is there much fibrous tissue, whereas many fields consist almost entirely of epithelial cells. There is no necrosis or inflammatory reaction within the neoplasm itself, but there are a few lymphocytes in the tissues about the tumor.

The neoplastic epithelial cells are arranged in large sheets and cords and also in small irregular masses (Fig. 2). There is no constant configuration. The individual cells in general have poorly defined walls and a moderate amount of cytoplasm. The nuclei are round to slightly oval, slightly hypochromatic and quite uniform in size; many have a prominent nucleolus. Mitotic figures are few in number. Within some of the masses of epithelial cells there is a hint of acinar formation. In these areas the cells tend to surround a small lumen, which is either empty or contains a small globule of hyaline-appearing material. In other places a short stretch of high columnar cells is

FIGURE 2.

arranged along a collagenous streak. In many places, including several spots along the capsular surface, the neoplastic cells infiltrate the collagenous stroma.

Diagnosis: adenocarcinoma of breast, Grade II.

The diagnosis of carcinoma was confirmed by Drs. Shields Warren, Charles F. Geschickter, Tracy B. Mallory and Benjamin Castleman.

SUMMARY

An authenticated case of cancer of the breast in a ten-year-old girl is reported.

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THE TREATMENT OF LOBAR PNEUMONIA WITH SULFATHIAZOLE AND SULFAPYRIDINE*

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IN AUGUST, 1939, Fosbinder and Walter[1] reported the preparation of sulfathiazole, a derivative of sulfanilamide. Shortly thereafter Rake et al.,[2-4] in a series of articles, reported the results of animal experiments using this new drug, the toxicity of which was in general found to be slightly less than that of sulfapyridine, the principal pathologic change being renal damage. The two drugs were shown to be equally effective against pneumococci. These studies indicated that of the two, sulfathiazole is more rapidly absorbed and excreted. Flippin et al.[5, 6] confirmed the latter finding in human beings. They also noted that kidney function was depressed in the majority of patients receiving the drug, and that nausea and vomiting was present in only 14 per cent. Long[7] expressed the opinion that sulfathiazole is approximately as effective as sulfapyridine in the treatment of pneumonia, and that the vomiting is definitely less. He mentioned 1 case of transient anuria and azotemia occurring during its administration. Flippin[8] has since reported 100 cases of pneumonia treated with sulfathiazole, with good results and no outstanding toxic symptoms.

MATERIALS AND METHODS

The present study deals with 60 patients with lobar pneumonia admitted to the Rhode Island Hospital during the first three months of 1940. Alternate cases received sulfapyridine and sulfathiazole.¶ These two groups were comparable in the average duration of their disease prior to admission, which was three days in both cases. The average of the patients in the sulfapyridine-treated group was fifty-two, as compared with forty-five in those treated with sulfathiazole. The diagnosis was confirmed by x-ray examination in all cases. Eighty per cent of the cases showed typable pneumococci. The sulfathiazole dose was 4 gm. initially, followed by 1 gm. every four hours for forty-eight hours, and thereafter 1 gm. every six hours until resolution was well under way. The dosage of sulfapyridine was similar, except that in most cases the initial dose was 6 gm. Occasionally the sodium salts of both drugs were used intravenously. Other routine measures consisted of blood cultures on admission, frequent determinations of the levels of the drugs in the blood, and oxygen administration when needed. Serum, in adequate dosage, was given to 4 patients receiving sulfapyridine, and to 5 receiving sulfathiazole.

RESULTS

The mortality was 10 per cent in each group. The relation of these deaths to some factors influencing the prognosis is shown in Table 1.

In comparing the temperature drop in response to the two drugs it was found that a prompter fall occurred in cases treated with sulfapyridine. However, at the end of forty-eight hours approximately the same number were afebrile in the two groups (Table 2).

TABLE 1. *Prognostic Factors.*

DRUG	NO. OF CASES	DEATHS	POSITIVE BLOOD CULTURE	PATIENTS OVER 60 YR.	TYPE 3 CASES	SERUM TREATMENT
Sulfapyridine..	30	3	3	10	6	4
Sulfathiazole..	30	3	5	4	2	5

TABLE 2. *Antipyretic Effects.*

DRUG	NO. OF CASES	TEMPERATURE FALL TO NORMAL WITHIN 24 HR.	WITHIN 24–48 HR.	TOTALS
Sulfapyridine....	30	10	10	20
Sulfathiazole....	30	5	13	18

The increased rapidity of temperature drop in the sulfapyridine group may possibly be related to the higher blood levels of this drug that we obtained. The average maximum level of sulfapyridine was 6.6 mg. per 100 cc. free and 10.3 mg. total as opposed to 5.2 mg. free and 6.8 mg. total of sulfathiazole. As can be seen from these figures, there is less tendency to conjugation in the case of the latter drug, a fact that has previously been noted by several observers.[2-4, 7]

Complications were not prominent in either group. Jaundice present on admission and gradually clearing under treatment was noted in 1 case in each group. Empyema and sterile effusion each occurred in 1 case among the patients receiv-

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¶The sulfathiazole was supplied through the kindness of Dr. George Harrop, of the Squibb Institute for Medical Research, New Brunswick, New Jersey.

ing sulfathiazole, and sterile effusions were noted in 3 patients given sulfapyridine. The toxic reactions found in the two groups are shown in Table 3.

One difference immediately apparent is the decreased tendency to nausea and vomiting seen with sulfathiazole as compared with sulfapyridine.

TABLE 3. *Toxic Reactions.*

TOXIC SYMPTOMS	SULFAPYRIDINE	SULFATHIAZOLE
Nausea and vomiting	18 (60%)	9 (30%)
Drug fever	1	2
Red blood corpuscles in urine	1	7
Leukopenia	0	3
Rise in blood urea nitrogen	1	3
Rash	0	2

Leukopenia was encountered in 10 per cent of the patients receiving sulfathiazole. In 1 case the white-cell count dropped from 20,000 to 2900 in two days, and in the other two the lowest points reached were 3800 and 1900 respectively. In all three the counts promptly returned to normal on discontinuance of the drug, and there were no related symptoms. A scarlatiniform rash and a papular rash were noted in 2 patients treated with sulfathiazole.

The 4 patients showing a marked rise in blood urea nitrogen during treatment warrant detailed consideration. The only such patient in the sulfapyridine group was a fifty-two-year-old man with an untyped pneumonia involving the right lower lobe. He received the usual dosage of drug for five days until a rise in blood urea nitrogen from 22 mg. per 100 cc. on admission to 64 mg. on the fifth hospital day occasioned withdrawal of the drug. During this time the temperature, pulse and respirations were normal, having fallen in the first twelve hours after admission. The patient was receiving adequate fluids. After drug treatment was stopped the blood urea nitrogen fell promptly to 17 mg. per 100 cc. six days later, and he made an uneventful recovery. Blood levels of the drug were high, being 9.8 mg. per 100 cc. free and 14.4 mg. total on the day after the drug was omitted. There was no oliguria. Urine showed a + test for albumin, a few granular casts and a moderately low specific gravity.

The 3 patients receiving sulfathiazole who showed marked increase in the blood urea nitrogen all died, constituting the only deaths in this group. In 1 case the drug could not be implicated. This patient was a seventy-nine-year-old woman with a Type 3 left-lower-lobe pneumonia, who was critically ill on admission and showed signs of spread despite treatment with sulfathiazole and 200,000 units of rabbit serum. She died on the fourth hospital day. The blood urea nitrogen was 74 mg. per 100 cc. on the day after admission and rose to 82 mg. twenty-four hours later. One urine specimen showed a + test for albumin. The fluid output was not measured because of incontinence. Sections of the kidneys removed at autopsy showed some arteriolar sclerosis and a few small focal scars consistent with a mild arteriolar nephrosclerosis. There were no significant acute glomerular or tubular changes. In this case high blood levels of the drug were also found, reaching 12.2 mg. per 100 cc. free and 15.9 mg. total.

The second patient was a fifty-seven-year-old man with a Type 18 right-lower-lobe pneumonia, who ran a high fever uninfluenced by the administration of 23 gm. of sulfathiazole and 200,000 units of rabbit serum until death on the twelfth hospital day. The blood urea nitrogen showed a steady increase from 18 mg. per 100 cc. on admission to 139 mg. two days before death, because of which the drug was discontinued on the fifth hospital day. The urinary output had been steadily dropping from the fourth to the seventh hospital day, when the patient developed grossly bloody urine, followed by almost complete anuria. Catheters were passed up both ureters without meeting any obstruction. The two urine sediments examined on admission had been completely normal, and at no time were crystals found in the urine. Blood levels of the drug were high, — up to 10.1 mg. per 100 cc. free and 14.0 mg. total, — with a later shift to the conjugated form after omission of the drug. Unfortunately permission for an autopsy was not obtained.

The third patient was a fifty-one-year-old woman with a right-lower-lobe pneumonia and an admission blood culture positive for Type 14 pneumococcus. Her response to sulfathiazole treatment was immediate, the temperature falling to normal in thirty-six hours and a blood culture becoming sterile. However, the temperature rose again on the eighth hospital day, reaching 106°F., with signs of spread to the other lung. Anuria developed on the eleventh day, the blood urea nitrogen thereafter rising progressively from 12 to 92 mg. per 100 cc. Despite withdrawal of the drug at the onset of anuria, the blood levels of sulfathiazole rose thereafter to 9.1 mg. per 100 cc. free and 13.7 mg. total. Ureteral catheterization was carried out without effect. Coincidentally with the second rise in temperature the patient developed a papular rash over the face, arms and legs. At autopsy there was widespread consolidation of both lungs. The ureters were patent, and the kidneys were soft and reddish. The microscopic changes in the kidneys, examined by Dr. Robert Williams, were as follows:

The glomeruli are everywhere relatively intact. There is extensive fatty metamorphosis of the convoluted tubular epithelium, as shown by epithelial swelling and minute vacuoles throughout the cytoplasm. Here and there in an isolated tubule there is necrosis of the epithelium, sometimes associated with infiltration by polymorphonuclear leukocytes, lymphocytes and large mononuclear cells. This cellular infiltration occurs both within the tubular lumen and in the surrounding interstitial tissue. The collecting tubules are frequently filled with hyaline casts, occasionally with polymorphonuclear leukocytes, and in other places are packed with desquamated epithelium. There is marked lymphocytic infiltration of the wall of the calyx and hyperplasia of its lining epithelium. The epithelium of the tubules at the junction of the cortex and pyramids is frequently packed with granules and aggregates of yellow pigment. The blood vessels are normal.

Discussion

The above results are obviously based on too small a series to be in any way conclusive, but indicate that sulfathiazole is approximately as effective as sulfapyridine in treating pneumococcal pneumonia in man. The slightly more rapid defervescence seen in the majority of the sulfapyridine-treated group certainly cannot be offered as an argument in favor of using this drug in preference to the other. The relative lack of nausea and vomiting in patients treated with sulfathiazole is a definite point in its favor, and the slightly diminished tendency of this drug to conjugation is of at least theoretical advantage.

On a further study of the toxic symptoms, other than nausea and vomiting, will probably depend the ultimate evaluation of the two drugs. Our findings are at variance with other reports in that leukopenia and anuria with uremia occurred with relative frequency in patients treated with sulfathiazole. The incidence of leukopenia may have been purely accidental, and it is possible that the cases of renal shutdown described above may have resulted from an overwhelming infection with toxic kidney damage, and not from any action of the sulfathiazole. However, none of the patients who died following the administration of sulfapyridine showed any suppression of urine, or uremia. Until more is known of the effect of sulfathiazole on the kidney, it seems obvious that renal function should be watched closely during its administration. In doing this, a study not only of the urine itself but of the daily fluid output and blood urea nitrogen seems essential.

Conclusions

The results in 30 cases treated with sulfathiazole and a like number treated with sulfapyridine under the same conditions are reported.

The mortality was 10 per cent in each group.

The therapeutic effectiveness and toxic manifestations of the two drugs are discussed.

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REPORT ON MEDICAL PROGRESS

CARDIOLOGY: I. THE MANAGEMENT OF CARDIAC PATIENTS WHO REQUIRE MAJOR SURGERY. II. THE TREATMENT OF CARDIAC ARRHYTHMIAS*

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I. THE MANAGEMENT OF CARDIAC PATIENTS WHO REQUIRE MAJOR SURGERY

THE following problems confront the physician when his patient with heart disease develops a condition demanding surgical intervention: Is the diagnosis correct, or are the symptoms and signs due to a cardiac condition requiring medical rather than surgical treatment? In view of the cardiac condition, is the life expectancy sufficient to permit the patient to experience the beneficial results of surgery? What is the additional hazard imposed by the presence of heart disease? Is it such as to present an absolute contraindication to the particular operative procedure? By what means, before, during and after the operation, can the risk be reduced? The knowledge upon which these decisions must be based covers practically the entire domain of medicine and surgery; the close collaboration of surgeon, physician and anesthetist is essential.

It is worthwhile to review in the light of recent contributions two main problems confronting the physician when he considers the advisability of surgery in a cardiac patient. What is the additional hazard imposed by the cardiac condition? How can the stress of operation be minimized by preoperative and postoperative management?

The Increased Hazard of Surgical Operations in Patients with Heart Disease

The patient with heart disease who is not confronted with the necessity of surgical intervention lives constantly under an increased hazard. Knowledge of the degree to which this danger is heightened by operation is essential in weighing the risk of non-interference against the risk of surgical intervention.

The following opinion of Marvin[1] in 1928 has received further support in the intervening years: "For purposes of anesthesia and operation a heart that is damaged but that is carrying on an adequate circulation under normal conditions of life is the equivalent of a normal heart." The distinction between heart disease and heart failure must be clearly kept in mind.[2] The added risk due to heart disease is generally proportional to the degree of decrease in the cardiac reserve. Certain conditions are exceptions: syphilitic heart disease with aortic insufficiency, complete heart block as a manifestation of any type of heart disease, aortic stenosis and angina pectoris.[1, 3] Patients with these disabilities are prone to sudden death, and it is consequently impossible to predict the course of events during and after operation. The existence of a considerable risk must be recognized, even though none of the usual contraindications are present.

Patients with congestive failure. The success with which adequate preoperative treatment may convert even those patients with gross evidence of congestive failure into less formidable risks was shown by a group of 144 patients reported by Hamilton.[4] All had definite signs of congestive failure on entry to the hospital and had major surgical operations; there were but 8 (5.5 per cent) operative deaths. In each case, every effort was made to relieve failure, and when evidence of congestion had disappeared, a further prolonged preparatory period of bed rest was employed. Hamilton advises bed rest whenever possible for at least three weeks after complete subsidence of decompensation, however mild. A similar mortality rate for such patients was reported by Butler, Feeney and Levine.[5] The presence of adequately controlled, persistent auricular fibrillation did not materially increase the operative risk. Auricular fibrillation and mitral stenosis predispose to the occurrence of embolism, but there is no acceptable evidence that, in the absence of congestive failure, this predisposition is heightened by operation.

Patients with rheumatic heart disease. In patients with mitral stenosis or other evidences of rheumatic fever, past or present, the reactivation of subclinical or latent rheumatic infection by operation or, indeed, by accidents involving fractured bones or sprained joints has been observed.[6] Subclinical rheumatic fever may be denoted by slight fever, repeated leukocyte counts of above 10,000, elevated heart rate, increase in sedimenta-

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tion rate and electrocardiographic changes such as prolongation of the auriculoventricular conduction time. In decisions regarding the most opportune time for elective procedures, this interrelation between operations and activation of rheumatic fever assumes significance.

Patients with angina pectoris or healed myocardial infarction. The recent report by Brumm and Willius[7] of their experience in 257 cases of coronary arteriosclerosis is a significant contribution. Only those patients were included who had undergone major operative procedures such as cholecystectomy, partial gastrectomy or posterior gastroenterostomy, transurethral prostatic resection, total abdominal hysterectomy or thyroidectomy. Thirty-two of their 257 patients had healed cardiac infarcts at the time of operation; in the remaining cases, angina pectoris had existed for an average of 3.1 years. The majority of these patients with advanced coronary sclerosis and serious surgical conditions were of advanced years, the mean age being 60 years. Half these cases showed significant electrocardiographic abnormalities such as incomplete or complete bundle branch block, complete heart block, auricular fibrillation, or significant T-wave negativity. One hundred cases (39 per cent) had well-marked hypertension.

The degree to which the increased hazard imposed by major surgery in such obviously ill patients can be reduced by skillful medical and surgical care is shown by the fact that only 11 cardiac deaths occurred (4.3 per cent). Seven deaths were due to coronary thrombosis with acute cardiac infarction, and 2 others occurred abruptly without apparent thrombotic occlusion. The authors properly emphasize that their experience should not instill false optimism, since the low incidence of fatality resulted from careful preoperative study, judicious selection, expert administration of anesthetics and skillful surgery. Operation was confined to those cases presenting unmistakable indications. The authors caution that it is of paramount importance that the surgeon insist on limiting the operation to the procedure planned in advance and avoid undertaking additional operative steps that might be justifiable in a patient without heart disease.

Surgery in relation to acute myocardial infarction. Patients with acute manifestations of coronary disease are poor operative risks, and surgery should not be undertaken except in extreme emergencies. Necessary operations may be performed, however, about three months following acute myocardial infarction when the patient is ambulatory and the infarct has apparently completely healed. According to the studies of Mallory, White and Salcedo-Salgar,[8] the healing process may usually be considered complete by that time.

Postoperative coronary thrombosis is one of the complications that cardiac patients, especially those in the older groups, may develop. This extremely dangerous complication dispels any optimistic view regarding recovery from the operation and demands the most painstaking care. A recent study by Master, Dack and Jaffe[9] lends support to the belief that operations may precipitate attacks of postoperative thrombosis. The authors have found several strong reasons for this opinion. It is apparent from their study that, emergencies excepted, if operation is to be undertaken in patients over fifty years of age, the cardiac status should be carefully appraised, and that when operation is considered advisable, special care must be taken to minimize shock and dehydration and to avoid infection. That shock following operations, hemorrhage and other states may precipitate acute coronary occlusions is further supported by a recent clinical and pathologic study of 350 consecutive, unselected, necropsied patients.[10] Eleven cases of multiple fresh coronary occlusions and 38 cases of single fresh coronary occlusions were found. Shock, with its attendant fall in blood pressure, dehydration and so forth, appeared to be a precipitating factor in all cases of multiple fresh coronary occlusions and in half the cases of single fresh occlusions; operation and its complications were responsible for shock in a significant number.

Since the introduction of insulin in the treatment of diabetes, the arteriosclerotic complications of that disease have become the chief cause of death in diabetes. The high incidence of acute coronary thrombosis in diabetic patients has been pointed out by several authors.[11, 12] It is therefore wise for the physician to warn surgeons contemplating operation on older diabetic patients, both male and female, of the possibility of precipitating an attack of coronary thrombosis and the importance of avoiding shock or a fall in blood pressure from any cause. The dangers of hypoglycemia in precipitating acute myocardial infarction in such patients should be particularly kept in mind.

Preoperative and Postoperative Management of Cardiac Patients

The frequency with which immediate operation is considered necessary has declined greatly in recent years. In the vast majority of cases an opportunity for preoperative preparation of the patient is available.

Sedation. The preoperative use of barbiturates such as phenobarbital in ¼-gr. or ½-gr. doses three or four times daily to lessen apprehension and its effects on the cardiovascular system has

won widespread adoption. Larger doses, such as 1½ to 3 gr. of phenobarbital, Sodium Amytal or Pentobarbital the evening before operation, and again immediately prior to operation, are commonly administered. Not infrequently, however, when the larger doses are given and particularly when morphine is also administered, the synergistic effect of a general anesthetic may result in dangerous consequences during the course of the operation. Delayed absorption of medication by mouth may cause the action of the drug to appear during operation, with anoxemia and resulting arrhythmias or vasomotor collapse.

In the administration of sedatives, sufficient dosage should be employed to produce drowsiness; narcosis, however, is to be avoided. The use of the smaller rather than the larger dose of the barbiturates mentioned above is usually advisable. If the patients are still alert or nervous immediately before operation, ⅙ or ¼ gr. of morphine may be injected subcutaneously.

When sedatives or opiates are administered for the first time, one occasionally discovers the presence of an idiosyncrasy, the patient becoming excited instead of drowsy. Since some cardiac patients will not withstand complications that more normal subjects might easily surmount, such untoward and even dangerous occurrences must be avoided by administering, whenever possible, several days before operation, test doses of all medicines that are to be used during the immediate preoperative and postoperative course. This procedure will make it possible to observe the nature of the reaction and gauge the optimum dosage with minimum hazard to the patient.

Body fluids and electrolytes. The full significance of the dehydration that may result from insensible loss of water, from vomiting and diarrhea and from other causes has been appreciated only in recent years through the observations of Gamble and his associates[13] and of Coller and Maddock.[14] The nature and amounts of fluid to be administered, which have been discussed elsewhere in this series of reports,[15] should result in an output of urine of at least one liter a day.

Cardiac patients are all too frequently subjected to vigorous diuretic medication with restriction of salt and fluids before operation, only to receive, according to routine orders a few hours later, large quantities of saline solutions by vein or by hypodermoclysis. *No specific routine can be followed in respect to cardiac patients.* If, despite treatment before operation, slight congestion of the lungs and evidences of edema are still present, the physician may properly consider that the patient has somewhat more than the normal available reserves of electrolytes and fluid that may be utilized in replacing the loss occasioned by operation. The findings on physical examination, the amount of perspiration, the amount of urinary output and the subjective degree of thirst experienced by the patient are important guides in deciding the amount of fluid to be administered. If the administration of fluids is indicated, the avoidance of heavy sedation and prolonged narcosis may enable the patient to take the necessary fluids by mouth, thereby eliminating the pain and discomfort of hypodermoclysis and the resultant effects on the cardiovascular and central nervous systems.

If fluids are given intravenously, the amounts and the rate at which they are introduced must be carefully supervised. The occurrence of pulmonary edema and of angina pectoris in cardiac patients as a result of the intravenous administration of fluids is not rare. An abnormally great and prolonged rise in venous pressure following the injection of 1500 cc. of normal saline at a rate of approximately 50 cc. a minute has been observed in patients with heart disease.[16] Postoperative studies of the dynamics of the circulation in patients without heart disease have shown that if 500-1500 cc. of physiological saline, or 5 per cent glucose solution in physiological saline are injected at rates of less than 20 cc. a minute, very slight changes in the cardiovascular functions result.[17] The blood volume is usually somewhat increased. When intravenous administration of fluids to cardiac patients is indicated, rates of less than 15 cc. a minute avoid these unnecessary hazards. Aside from their immediate effect, intravenous infusions that continue or are repeated over a period of several days, as may be necessary after prostatectomy, favor the development of edema, both peripheral and pulmonary, even though the fluid is given at very slow rates. The lowering of the plasma-protein level, due to plasma dilution, vasodilatation due to increased blood volume, and the tendency toward increased venous pressure by operating together over a period of days, may result in clinically perceptible edema.[17] Postoperative nutritional edema may favor such an occurrence.[18]

Digitalis. The almost routine digitalization of patients over the age of fifty has received diminishing acceptance. No trustworthy evidence indicates that any useful purpose is served thereby in patients who do not have congestive heart failure or auricular fibrillation. In general the same indications for digitalis apply to the preoperative cardiac patient as to the cardiac patient in whom surgery is not contemplated. In patients with auricular fibrillation, somewhat greater than usual

amounts may be employed because of the disproportionate rise in ventricular rate that may occur under stress.[19]

Anesthesia. The anesthetist is to be considered as a consultant rather than as a technician and should participate in discussions of the particular problems offered by the individual patient. Precautions should be undertaken to prevent atelectasis. Large doses of narcotics before and after operation are undesirable, and atropine should be used only in small doses or omitted entirely from the preoperative medical regime. To protect the liver against the fat-solvent anesthetic agents and to prevent general anoxia with its deleterious cardiovascular effects, the use of a high percentage of oxygen with the inhalation of anesthetics is advantageous.[20] The judicious use of preoperative sedation reduces the concentration of gaseous anesthetics necessary for a given level of anesthesia and thereby permits higher concentrations of oxygen to be used simultaneously.[21] The use of nitrous oxide anesthesia is particularly hazardous in cardiac patients for operations of long duration because of the frequency of anoxia. The newer developments in the administration of spinal anesthetics have increased the applicability of this form of anesthesia. The danger of a fall in blood pressure, particularly in patients with marked hypertension, should be kept in mind. While statistics indicate that postoperative pulmonary complications are more frequent in patients after spinal anesthesia, this result can be attributed in part to the fact that spinal anesthesia usually is reserved for the elderly subjects with pulmonary disease. With these considerations in mind, the choice of anesthesia for the cardiac patient is much the same as for the non-cardiac patient; ether continues to be the most widely used anesthetic. Operation during the late hours of the morning or even in the afternoon may be advantageous in elderly cardiac patients with coincident pulmonary bronchiectasis, who raise considerable amounts of sputum on awaking in the morning.

Oxygen. Prophylactic oxygen therapy should be considered after operation in all cases in which the cardiac reserve is limited. With modern simplified methods of oxygen therapy, such as the B.L.B. mask and the face tent, oxygen can be used economically and more satisfactorily than formerly.[22] Apprehension may be minimized by administering oxygen preoperatively to such patients for short periods of time to accustom them to this procedure.

Nitroglycerin. The prophylactic use of nitroglycerin has not been so widely utilized as it deserves.[23] The patient with angina pectoris whose attacks respond to this medication may benefit greatly by receiving 1/500 gr. under the tongue every half hour preoperatively, and if the operation is to be done with local anesthesia, during operation as well.

Prevention of Postoperative Complications in Cardiac Patients

Particular consideration must be given to certain complications which are especially prevalent in cardiac patients.

Pulmonary complications. The incidence of these justly dreaded complications can be reduced by the following measures: eliminating pulmonary congestion of lungs, preoperatively; obviating prolonged narcosis; avoiding the administration of unduly large amounts of fluids postoperatively or of unnecessarily large doses of sedatives; removing bronchial secretions with a catheter or the use of postural drainage in certain cases; frequent changing of the position of the patient; encouraging deep breathing; and avoiding tight abdominal binders and distention. In all patients with heart disease and especially those who have a limitation in their cardiac reserve, a decreased incidence of pulmonary embolism is believed to have been accomplished by massage and by active and passive motion of the limbs. The use of helium and oxygen mixtures, first introduced by Barach in 1934, has received favorable comment when used in the occasional instances of obstruction to the passage of air in the respiratory passages.[22] Oxygen therapy should be used more freely for any postoperative complication occurring in cardiac patients. Morphine lowers both the rate and amplitude of respiratory excursions; its use in doses that usually cause no ill effects may lead to atelectasis and bronchopneumonia in the elderly cardiac patients with pulmonary emphysema.

Intestinal distention. Cardiac patients are especially prone to develop intestinal distention. The inhalation of pure oxygen as suggested by Fine and Starr[24] will not only benefit the intestinal distention, but will also tend to obviate anoxemia and its effects on the heart. Intractable distention in these patients may occasionally justify the use of an inlying Levin tube with suction applied.

Malnutrition. Cardiac patients not infrequently manifest hypoproteinemia as a result of anorexia, albuminuria and the dilution of the blood plasma that accompanies congestive failure. Blood protein may assume normal values after diuresis in some cases. It should be remembered that in the presence of an increased capillary permeability such as may accompany congestive failure, the administration of large quantities of saline solutions may result in great harm. The use of a well-balanced

diet and the transfusion of plasma or blood are effective. The importance of normal nutritional reserves and the particular effect of thiamin deficiency on the heart must be kept in mind.[25]

Cardiac complications. The incidence of acute myocardial infarction and the occurrence of shock, dehydration or fall in blood pressure from any cause as a contributing factor have already been discussed. The effectiveness of Paredrine[26] and other sympathomimetic drugs in preventing hypotension in the course of spinal anesthesia and in restoring the blood pressure to normal levels in the treatment of peripheral vasomotor collapse has been reported. Doses of 10 mg. given intramuscularly, and repeated according to the effect on blood pressure, are to be recommended. Unlike amphetamine (Benzedrine), Paredrine does not cause psychic stimulation, and in contrast with ephedrine, no increase in the output of the heart occurs. Untoward effects on the heart are not caused by therapeutic doses.[26]

Paroxysmal auricular and ventricular tachycardia, auricular fibrillation and various degrees of heart block may occur during operation. Although cardiac arrhythmias frequently occur in patients without heart disease, there is a greater incidence among those with abnormal hearts. The treatment of these disorders will be discussed later.[27]

Drugs Commonly Used Preoperatively and Postoperatively That May Affect the Heart Adversely

Certain medicinal agents, commonly used in the postoperative treatment of patients, have additional effects on the cardiovascular system that may lead to dangerous or even disastrous consequences. Aside from sedatives and other agents discussed elsewhere in this report, the following may be cited:

Extracts of the posterior lobe of the pituitary gland (Pituitrin, Pitressin and so forth). When these are used for treating abdominal distention they may, through vasoconstrictor action, precipitate severe angina pectoris and collapse. In cardiac patients with intestinal distention and oliguria, Pituitrin is not infrequently given for the intestinal distention, without a realization that it likewise tends to accentuate the oliguria.

Carbon dioxide mixtures. The inhalation of such mixtures invoked because of intractable hiccough, particularly after genitourinary operations, imposes a strain on the heart, since the ventricular rate is increased and the blood pressure and minute volume output of the heart become somewhat elevated, particularly if concentrations of more than 5 per cent are utilized.[28]

Ergot. The administration of ergot to produce uterine contraction after dilatation and curettage not infrequently leads to severe cardiac pain.

Atropine sulfate. When atropine sulfate is used to lessen the bronchial and upper respiratory secretions, it is not always realized that, through the inhibitory effect on the vagus nerves, undue elevation of the ventricular rate may occur, particularly in patients with auricular fibrillation.

Insulin. Degrees of hypoglycemia that would be tolerated readily by most patients may precipitate the characteristic manifestations of acute myocardial infarction in the presence of coronary arteriosclerosis.

Adrenalin. Particularly in patients with angina pectoris due to coronary arteriosclerosis, and even in the presence of asymptomatic coronary narrowing or occlusion, adrenalin may incite severe cardiac pain and occasionally may produce collapse and death.

Cocaine and novocain. The ready absorption of cocaine and novocain when applied to the upper respiratory passages may cause the inception of collapse or of cardiac arrhythmias, and at times of ventricular fibrillation and death. This danger is present in normal persons, but particularly in patients with an irritable myocardium resulting from the reduction in coronary blood flow by coronary arteriosclerotic lesions.

The use of these agents is not necessarily contraindicated in patients with heart disease; a realization of their effects on the cardiovascular system and the possible hazards involved will suffice to prevent their indiscriminate and unwise employment when their beneficial effects are desired.

II. The Treatment of Cardiac Arrhythmias

Disorders of cardiac rhythm constitute one of the most frequent conditions that confront the physician. Knowledge of the precise mechanisms of the various arrhythmias is essential; although certain irregularities may be regarded with equanimity and may require no treatment, others necessitate specific therapy, since they interfere with the well-being of the patient and may even threaten his life. The action of the drugs to be used must be understood, since medication which terminates one arrhythmia may be ineffective or even dangerous in another.

The most important types of cardiac arrhythmias are as follows:

Extrasystoles, auricular or ventricular
Paroxysmal auricular tachycardia

Paroxysmal ventricular tachycardia
Auricular flutter
Auricular fibrillation
Heart block with Adams-Stokes attacks

Drugs that exert a useful effect are as follows:

Quinidine
Digitalis
Acetyl-beta-methylcholine (Mecholyl)
Emetics, such as syrup of ipecac

The clinical recognition, electrocardiographic characteristics, and the mechanism of the various arrhythmias are clearly delineated in the various cardiological texts. Several reports have clarified certain aspects of these conditions and will be summarized. Gold[29] states that although a differential diagnosis of the various arrhythmias can be made solely by clinical means, an electrocardiogram is usually necessary to establish the diagnosis and to ensure safe and effective treatment. The routine tracing may fail to be of value; however, a tracing should be made *before* and *during carotid-sinus pressure*. A patient with a rapid regular tachycardia of 150-175 a minute may have either sinus tachycardia, paroxysmal auricular tachycardia, auricular flutter or ventricular tachycardia. The standard tracing may be equivocal; the auricular deflections may be buried in the ventricular deflections. Application of carotid-sinus pressure may clarify the diagnosis. If auricular and ventricular contractions are slowed, the diagnosis of sinus tachycardia is evident. If both auricle and ventricle are brought to a complete momentary standstill, the diagnosis of paroxysmal auricular tachycardia may be confirmed. If auricular flutter is present, the ventricular rate may be slowed, and the auricular deflections of 300 or more a minute may be readily seen. Carotid-sinus pressure may produce no effect on either the auricle or ventricle, in which case, and in the presence of other characteristics of the ventricular deflections, a diagnosis of ventricular tachycardia is indicated. If carotid-sinus pressure is not effective, ocular pressure, holding the breath at the end of deep inspiration, straining at the end of deep inspiration with the glottis closed, or lying across the bed with the head hanging over the side of the bed, may be of assistance.

Extrasystoles

This, the commonest of all cardiac irregularities, frequently occurs unassociated with organic heart disease in nervous, apprehensive patients. In occasional cases, when numerous extrasystoles mask the underlying sinus rhythm, differentiation from auricular fibrillation may be difficult without the aid of the electrocardiograph. Reassurance, the prescription of a rational regime of life, psychotherapy, the avoidance of tobacco, tea and coffee, and the administration of repeated small doses of sedatives are frequently effective. In refractory cases, quinidine sulfate, 3.0–5.0 gr., on awaking and every hour or five hours until bedtime is to be recommended. Extrasystoles of ventricular origin may predispose patients with coronary arteriosclerosis to attacks of paroxysmal ventricular tachycardia; quinidine should be employed. Although digitalis in such patients may increase myocardial irritability and hence increase the number of extrasystoles, in others the favorable effect on the heart results in abolition of the extrasystolic irregularities. Partial digitalization by relatively small doses, such as 1.5 gr. two or three times daily, with careful observation of the results of treatment, is advisable under such circumstances. The use of repeated small doses of the barbiturates, such as phenobarbital, ¼ gr. three or four times daily, is a valuable adjunct.

Paroxysmal Auricular Tachycardia

This arrhythmia frequently occurs in the absence of organic heart disease, is sudden in onset, lasts a few seconds to hours or even days and is characterized by its extraordinarily constant rate of 150–200 a minute. If the attacks are short and infrequent, no treatment is necessary. Carotid-sinus pressure, or one of its equivalents, previously mentioned, may terminate the attack if spontaneous subsidence does not occur. Since the attacks frequently cease spontaneously and are greatly influenced by emotional states, the physician attending a patient early in the attack should defer vigorous therapy and prescribe sedation, such as 5.0 gr. of barbital, 3.0 gr. of Sodium Amytal or 15-gr. tablet of triple bromides, to be followed by smaller doses in two or three hours until drowsiness occurs. If the attack persists, Mecholyl (acetyl-beta-methyl-choline), the most effective drug for this condition, may be administered, provided, however, bronchial asthma, angina pectoris, hyperthyroidism[30] or recently healed myocardial infarction is not present. Mecholyl is a powerful parasympathetic stimulant and not uncommonly produces flushing, salivation, profuse perspiration, nausea, vomiting and occasionally dyspnea, precordial pain or collapse. Because of these severe untoward reactions, cautious administration must be practiced. The patient should be recumbent during and immediately after the injection. Since Mecholyl is such a powerful agent and may cause drastic toxic reactions, it should never be given until a second syringe containing 1/50 or 1/100 gr. of atropine has been prepared and is immediately available. Atropine is an instantaneously effec-

tive antidote. Certain authorities advise intramuscular injection of atropine, but intravenous administration is usually preferable. Mecholyl should be injected subcutaneously or, in resistant cases, intramuscularly; *intravenous injection is extremely dangerous and should never be practiced.* An ampoule of Mecholyl Hydrochloride usually contains 25 mg.; this is dissolved in 0.5 or 1.0 cc. of water. The dosage is proportional to age and body weight. The average dose is 25 mg.; 10 to 20 mg. may suffice for patients ten to twenty years of age, whereas 50 or 60 mg. may be necessary in older, obese persons. The effect of the dose may be enhanced by vigorously massaging the area of injection and by applying carotid-sinus pressure from time to time.[31] Abrupt cessation of the attack should occur within fifteen minutes. A second or even third injection may be necessary at fifteen-minute to twenty-minute intervals. If the dosage is too large, the heart may manifest complete standstill for thirty or forty-five seconds.

Quinidine is antagonistic to Mecholyl, and if the patient has taken any quinidine within twenty-four hours of the time Mecholyl is given, the latter may fail even if the dose is larger than that ordinarily employed.[32]

If the use of Mecholyl is not considered advisable, emetics, such as syrup of ipecac in doses of 1 or 2 teaspoonfuls, may be used.[33] If the desired therapeutic result is not obtained, the dose may be repeated after one hour. Nausea and vomiting with their associated vagal activity usually terminate the attack of tachycardia. Apomorphine, 1/20 gr. by subcutaneous injection, has been suggested and not infrequently will accomplish the same result, but it must be considered a drastic measure.

Quinidine, in large doses (10 gr.) by mouth every two hours until a total of 30, 40 or even 50 gr. has been given, is often employed. Similarly, 7½ gr. of quinine dihydrochloride injected intravenously or intramuscularly after dilution with 20 cc. of fluid has been utilized. The toxicity of such large doses and the uncertainty of success have led to a less frequent use of quinine and its derivatives. Large doses of digitalis, although occasionally effective, are usually unsatisfactory.

Prevention of attacks of paroxysmal auricular tachycardia. Some patients are troubled by frequent recurrent attacks of tachycardia. Digitalis is frequently effective when full dosage is employed. If the patient has not received digitalis within ten days, 3.0 gr. may be given at six-hour intervals for three or four doses, and then 1.5 gr. two or three times daily until evidence of digitalization appears, such as anorexia or T-wave changes, following which a maintenance dosage should be employed. If digitalis is not effective, it should be discontinued, and quinidine sulfate should be prescribed in doses of 5.0 gr. on awaking and then every four or six hours until bedtime. If the patient is hypersensitive to quinidine or shows idiosyncrasies, such as diarrhea or nausea, the dosage should be decreased or the drug discontinued. The use of sedatives, psychotherapy and the avoidance of fatigue are important. The possibility of thyrotoxicosis must be considered.

Paroxysmal Ventricular Tachycardia

This disorder, although it is distinctly uncommon, is a serious condition, must be promptly recognized and must be treated with dispatch. Although far less frequent than paroxysmal auricular tachycardia, paroxysmal ventricular tachycardia is more commonly associated with serious myocardial disease, such as acute infarction, and may lead to ventricular fibrillation and death. The development of ventricular fibrillation is favored by digitalis, and the use of this drug is therefore definitely contraindicated.

Quinidine is effective and should be employed until toxic or therapeutic effects are evident. Because of the seriousness of the condition, it is usually advisable to begin with a dose of 10 gr. Its effect will be evident in two hours, at which time the dose can be repeated or increased. Larger and more frequent doses, although entailing a risk, may be indicated in desperate circumstances. Fahr[34] reports using as much as 5.5 gr. in five hours in one case. Dangerous defects of intraventricular conduction may occur; frequent electrocardiograms taken during treatment should be helpful in avoiding such complications.

In paroxysmal auricular tachycardia, the auricular rate remains remarkably constant until the abrupt lowering to normal. In paroxysmal ventricular tachycardia, however, the ventricular rate may vary several beats a minute. Quinidine may lower the ventricular rate, even though it does not abolish the abnormal rhythm. This is important, since, in cases with a ventricular rate approaching 200 or more, severe precordial pain or collapse may be experienced. Under such circumstances, lowering of the rate may dispel the pain, reduce the work of the heart and tend to prevent cardiac damage and the onset of ventricular fibrillation. Since this effect is related to the concentration of quinidine within the body, doses of 5.0 to 7.5 gr. of quinidine should be repeated every two hours, the ventricular rate and clinical condition serving as guides, until the therapeutic effects are attained or nausea, vomiting and so forth make lessening of the dosage imperative.

In the presence of vomiting or circulatory collapse, poor absorption from the gastrointestinal tract makes parenteral therapy advisable; quinine dihydrochloride may be used under such conditions.[35]

The prophylactic use of quinidine is indicated in patients with acute myocardial infarction who develop multiple ventricular premature beats. Similarly, in certain persons who are prone to develop recurrent attacks of paroxysmal ventricular tachycardia, quinidine in doses of 5.0 gr. administered four times daily is frequently effective.

Auricular Flutter

The auricle in this infrequent condition beats at a rate of 250–350 a minute as a result of waves circulating in a ring of muscle between the superior and inferior venae cavae. The rate of beating of the auricles is extraordinarily constant. The ventricular rate is frequently half that of the auricles, but may vary from time to time; in fact, an abrupt rise in ventricular rate due to a change from 4:1 to 3:1 or 2:1 block on slight effort may be of diagnostic importance. Quinidine and digitalis are the two effective drugs in the treatment of this disorder. Most authorities advise the initial use of quinidine alone. Large doses are usually required — 10 gr. every two hours for three to five doses are sometimes necessary. In the presence of rapid ventricular rates, however, digitalis should be utilized. By imposing auriculoventricular block, the ventricular rate may be controlled at normal levels, even though the flutter of the auricles persists. The dosage may be similar to that employed in paroxysmal auricular tachycardia. In some cases neither quinidine nor digitalis abolishes the arrhythmia, but the patient may continue a comfortable and normal life, with the ventricular rate satisfactorily controlled by digitalis.

The administration of digitalis frequently converts auricular flutter to auricular fibrillation. Normal sinus rhythm may occur spontaneously on withdrawal of digitalis or following the administration of quinidine.

In certain patients prone to recurrent attacks, quinidine may be useful when administered according to the plan outlined for patients with recurrent attacks of paroxysmal ventricular tachycardia.

Auricular Fibrillation

The indications and contraindications for the use of quinidine in restoring normal rhythm in patients with auricular fibrillation continue to be subject to a wide diversity of opinion. In general it has become increasingly clear that the abolition of auricular fibrillation by quinidine has very limited application; auricular fibrillation of long standing, cardiac enlargement, advanced mitral stenosis, active rheumatic infection and prior congestive failure contraindicate its use. Patients with persistent auricular fibrillation are better stabilized and more safely controlled by appropriate dosage of digitalis. The urgency of the situation will influence the speed with which the patient is digitalized; the plan of treatment is usually similar to that described above for the prevention of attacks of paroxysmal tachycardia.

In some patients after subtotal thyroidectomy for thyrotoxicosis, and in some with paroxysmal auricular fibrillation in the absence of congestive heart failure or organic heart disease, quinidine may be useful to abolish or prevent auricular fibrillation. If no idiosyncrasy to quinidine is manifest after a test dose, the drug may be administered in three doses of 5.0 gr. each every two or three hours for one day, giving four and then five or six doses on each succeeding day.

Complete Heart Block with Adams–Stokes Attacks

Most cases of complete heart block require no treatment, although digitalis is frequently given because of its beneficial effect on the myocardium. Occasionally patients suffer syncopal attacks when transitions from partial to complete block occur. Digitalis will maintain complete block and prevent such syncopal attacks. In a second group of cases, syncopal attacks occur in the presence of persistent complete heart block. In these patients the symptoms are due to a lowering of the idioventricular rate from 30 or 40 to 9 or 10 a minute.[29] Ephedrine in doses of ⅜ gr. four times a day may be effective. In some cases emotional factors are responsible for changes in the degree of block and thus give rise to Adams–Stokes attacks. Phenobarbital, in doses of ¼ gr. four times a day, may be more effective in preventing attacks in such patients than is digitalis, ephedrine or adrenalin.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26451

PRESENTATION OF CASE

A forty-two-year-old insurance broker entered the hospital complaining of a chronic cough and chest pain.

The patient felt perfectly well until eight weeks before admission, when he contracted a slight cold that cleared within a few days. One week later he suddenly noticed a sharp pain in the anterolateral portion of the left lower chest. His physician said that he had a cold, but the pain continued and within the next three days a cough with yellow sputum developed. Another physician made a diagnosis of bronchitis, put him to bed, and treated him with sulfapyridine. The symptoms continued, however, and the temperature rose to 101.4°F. Physical examination at that time showed a decrease in respiratory movement on the left, with inability to take a deep inspiration because of pain in the left lower chest that radiated to the adjacent upper quadrant of the abdomen. On this side there was dullness to percussion in the lower half, both anteriorly and posteriorly, and breath sounds were absent over these areas. X-ray examination revealed an irregular consolidation of the lower two thirds of the left lung; the tracheal and heart shadows were displaced to the right. The urine was normal, and the white-cell count 8500. Nothing was obtained on two pleural punctures. A diagnosis of unresolved pneumonia was made, and the patient was admitted to another hospital. Two weeks later the temperature had returned to normal, and x-ray study showed only a small area of consolidation in the left lower chest. He was about to be discharged, when the temperature rose again and continued in an irregular spiking manner finally steadying so that it was 100°F. each morning and 101 each afternoon. Several sputum examinations and one gastric lavage were negative for tubercle bacilli. On the thirty-sixth day of hospitalization and two days before he entered this hospital, the patient was referred to another institution for diagnosis. Here a bronchoscopic examination was performed, and abnormal findings were reported as follows:

> Mucopurulent secretions were encountered in the left stem bronchus and were aspirated. The upper-lobe orifice appeared normal, but the lower-lobe orifice, as well as the lower-lobe bronchus, was narrowed concentrically so that it was impossible to pass the full lumen of an S-40 bronchoscope; the diameter of this bronchus was reduced by 25 per cent. The mucosa of the bronchus was intact, although slightly reddened and edematous. The secondary divisions of the bronchus were visualized, and no neoplastic tissue was evident.

The patient was referred to this hospital. At the time of admission he had had no chest pain for three weeks and the cough and sputum, although still present, had improved greatly. He had lost about 20 pounds since the onset of the illness.

The patient had had the usual childhood diseases, including diphtheria at seven years. The family history was irrelevant.

Physical examination showed a well-developed and well-nourished man in no apparent distress. Examination of the heart was negative; the blood pressure was 115 systolic, 70 diastolic. There was no apparent diaphragmatic excursion. Dullness to percussion and diminished breath sounds were noted at the left lung base posteriorly, and fine rales were heard along the eighth, ninth and tenth ribs at the posterior axillary line. The physical findings were otherwise negative.

Examinations of the urine were negative. Examination of the blood showed a red-cell count of 4,960,000 with a hemoglobin of 11.9 gm. (photoelectric-cell technic), and a white-cell count of 21,500. The sedimentation rate was 55 mm. in one hour. The nonprotein nitrogen of the blood serum was 15 mg. per 100 cc. and the serum protein 6.9 gm. A blood Hinton test was negative. Microscopic examination of the sputum on three occasions failed to show tubercle bacilli. One of three sputum cultures grew a few colonies of beta hemolytic streptococci; the remaining two yielded the usual bacteria of the respiratory tract.

A fluoroscopic examination showed the left side of the diaphragm to be fixed, irregular and high. A shifting fluid level in the region of a sharply defined hemispherical shadow occupied the lateral aspect of the left base. This shadow was continuous with that of the diaphragm, and density in the region of the pleura simulated fluid. Two gas bubbles were present that shifted in position, one lying within the hemispherical shadow and the other just above and anterior to it. The bubble outside the hemispherical shadow was not seen in all the films, but the one within the hemispherical shadow increased in size after postural drainage. The sharply defined shadow was apparently a cavity, the walls of which varied from 4 to 10 mm. in

thickness. The heart was slightly displaced to the left, and a dense irregular shadow was seen along its left base. There were no mediastinal masses and no evidence of metastases, but scars in the right upper lobe suggested old tuberculosis. These findings, when compared with films taken three days previously in another hospital, revealed no appreciable change.

The third day after admission a bronchoscopic examination was performed. The larynx, vocal cords and trachea were normal. The carina was sharp, and the right tracheobronchial tree normal. The left-upper-lobe orifice was normal, but approximately 1 cm. below it the lower-lobe bronchus was distinctly narrowed. The narrowing was due to constriction in size rather than to swelling of the mucosa. Because of this constriction only two or three terminals could be visualized. No neoplasm could be seen, and the orifices exuded no secretion.

On the seventh hospital day an exploratory thoracotomy was performed.

Differential Diagnosis

Dr. Donald S. King: We do not have the early x-ray films from the outside hospital, but I assume from the description that the fluid in the left pleural cavity displaced the heart to the right, and that after the dry taps the fluid diminished greatly and the abnormal x-ray shadow was much smaller.

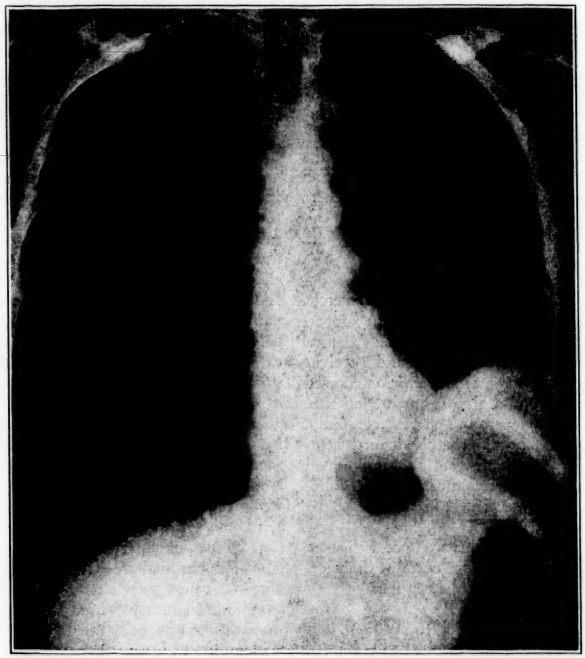

Figure 1. *Chest Plate Showing the Air Bubble in the Spherical Shadow in the Left Lower Chest.*

Dr. Aubrey O. Hampton: These are the films taken at a later date in the outside hospital. Our films, taken two days later, show the same findings. The gas bubble within the hemispherical shadow described at the left base shows very plainly (Fig. 1). The shadow is quite sharp, and is continuous with the diaphragm and pleural surface. The second gas bubble described is not easy to see. It was thought that the second bubble was farther forward than the first.

DR. KING: I shall assume, then, that there were two bubbles, one anterior and well away from the hemispherical shadow described, and the other within the shadow itself. Am I correct in this, Dr. Hampton?

DR. HAMPTON: Yes. The thickness of the wall of this cavity, as demonstrated by the shifting of the gas bubble, is given as 10 to 4 mm. I should say that it was even thicker than 10 mm. at its greatest width. The fixation of the diaphragm was described, and one can see the splenic flexure and the gas bubble in the stomach. There is no hernia. There is density in the left lung, along the left border of the heart.

DR. KING: We have settled the problem of the two bubbles and have Dr. Hampton's description of the thickness of the wall of the cavity. There is also, I believe, evidence of pleural involvement.

DR. HAMPTON: Obviously, yes, and pleural fluid.

DR. KING: Outside the mass?

DR. HAMPTON: Yes.

DR. KING: The story is one of a man who eight weeks before admission, following an upper-respiratory infection, developed cough, purulent sputum, irregular fever, pleural pain and a weight loss of 20 pounds. Laboratory examination showed a high white-cell count, a high sedimentation rate, apparently no foul sputum and no tubercle bacilli. X-ray examination showed a sharply defined, hemispherical shadow, which apparently communicated with the bronchus because after postural drainage there was a definite change in the size of the bubble.

DR. HAMPTON: The bubble was not visible by fluoroscopic examination before postural drainage.

DR. KING: Could it be seen afterward?

DR. HAMPTON: Yes.

DR. KING: So you are willing to say there was communication with the bronchus in that area?

DR. HAMPTON: Yes.

DR. KING: There was, then, a cavity containing fluid and communicating with a bronchus, but besides this there must have been fluid in the pleural cavity itself. I cannot conceive of a cyst-like cavity large enough to give the shadow originally described and later shrinking to the size of the shadow now under discussion.

From the description of the first bronchoscopic examination I believe that a small but otherwise normal bronchus was seen. In the report of the one done in this hospital no mention is made of involvement of the mucosa, of tumor outcropping or of pressure from outside the bronchus. Did you bronchoscope him, Dr. Adams?

DR. RALPH ADAMS: Yes. When Dr. Chamberlain bronchoscoped the patient outside the hospital, he found the same amount of narrowing as we found here and suggested verbally that edema might have been the cause of the narrowing. But when we bronchoscoped him the extent of the narrowing was exactly the same, and there was no edema.

DR. KING: That sounds like an abnormally small bronchus. I cannot make anything else out of it.

It seems to me that there are six possible explanations for the picture as presented. The mass could be a malignant tumor with central necrosis; we have had cases of carcinoma in which the tumor has broken down, discharged into a bronchus and presented the x-ray picture of a shifting fluid level, but I cannot remember any case in which there has been such complete breaking down and such free bronchial drainage from the necrotic cavity. Secondly, we could be dealing with bronchiogenic carcinoma and a pulmonary abscess secondary to bronchial obstruction, but the x-ray appearance is not that of typical abscess and the patient is not so sick as is to be expected in such cases; the anterior bubble described could be a small pulmonary abscess, but I do not believe that it is. A benign bronchial tumor, perhaps an adenoma, with a secondary abscess is also a possibility. This seems to me unlikely because bronchial adenomas are almost always seen in the larger bronchi through the bronchoscope, and they usually give a history of gradually increasing cough and hemoptysis and not the onset described in this case. True pulmonary abscess without pre-existing bronchial obstruction — another possible explanation — at times gives clear-cut round shadows almost indistinguishable from tumors, and such an abscess could be accompanied by a pleural effusion; in this case, however, there has been no foul sputum, and a non-putrid abscess with this x-ray picture is certainly rare. The fifth possibility is encapsulated empyema. In my experience such an empyema is associated with a foul pleural fluid and has developed only after the rupture of a small subpleural abscess; there is no evidence in the record of such an abscess or such severe symptoms as usually follow an empyema of this sort. This brings me to the possibility of a cyst which has become secondarily infected. I do not know how to explain the picture on any other basis. If it is a cyst, it may be congenital or "secretory." In the first case there is an anatomic abnormality present from birth, and in the second interference with drainage of the secretions may come about after birth. We have had one case of an infected

congenital cyst that was very much like the present one. The patient was operated on once for empyema but was later shown to have a congenital cyst with a complete congenital stenosis of the bronchus leading to the posterior portion of the left lower lobe. In today's case I am assuming that the bronchoscopy did show an anatomic variation of the left-lower-lobe bronchus that was associated with the presence of a congenital cyst in the area beyond the reach of the bronchoscope.

My diagnosis, then, is congenital cyst that has become secondarily infected and has led to a neighboring infection in the pleural space.

DR. TRACY B. MALLORY: Has anyone else a suggestion?

DR. EDWARD D. CHURCHILL: Why do you rule out empyema so lightly?

DR. KING: Because in my experience in cases like this there has always been a pre-existing pulmonary lesion that has led to a pleural fistula and empyema. Perhaps I should pay more attention to the possibility that an empyema ruptured into the bronchus from the outside.

DR. CHURCHILL: I find that a good many streptococcal empyemas develop bronchial fistulas.

DR. KING: Do they? Can a streptococcal empyema give this picture?

DR. CHURCHILL: I should think so.

DR. KING: Certainly the sharply defined shadow is not inconsistent with encapsulated pus.

DR. CHURCHILL: In referring to the description of the previous films, you said yourself that there was fluid in the pleural cavity.

DR. HAMPTON: Do you think the wall of this cavity is thicker than that of the congenital cyst you mentioned?

DR. KING: No. As I recollect the wall of the congenital cyst was quite thick in certain portions. Other types of cysts would have a thinner wall.

DR. CHURCHILL: I should say the walls of congenital cysts were very thin.

DR. MALLORY: I think that I should agree with Dr. Churchill. Anatomically they are thin. I do not know how they look by x-ray examination.

DR. KING: Look at this photograph of the proved congenital cyst.

DR. CHURCHILL: What is its thickness in millimeters, Dr. Hampton?

DR. HAMPTON: I have to admit that the wall is as thick as this one in some places, but very thin in others.

DR. KING: I grant you that, but I am sure that cysts proved at operation to be thin walled have given the x-ray appearance of thick walls. Here is an example.

DR. MALLORY: We have to count on Dr. Adams to tell us most of the pathology because, thanks to him, the patient survived.

CLINICAL DIAGNOSIS

Carcinoma of the left lung?

DR. KING'S DIAGNOSIS

Congenital cyst of lung, with secondary infection.

ANATOMICAL DIAGNOSIS

Encapsulated empyema.

PATHOLOGICAL DISCUSSION

DR. ADAMS: Dr. Lowrey F. Davenport and I saw the patient together in consultation during the summer when our chiefs were away. The atypical pneumonia, the variability of the clinical symptoms, the evidence of pleural involvement, the suggestion of abscess as indicated by the fluid level and the evidence of bronchoscopy of narrowing of the lower lobe bronchus made us think that this was a case almost identical with one we had previously seen in which at operation there was a thick-walled peripheral abscess secondary to primary cancer of the bronchus. That was our preoperative diagnosis.

At operation the pleura was found adherent laterally, as anticipated. It was edematous and thickened. When it was opened posteriorly the lower lobe was found collapsed, and where the incision was carried anteriorly, a circular abscess cavity was opened. It seemed that an ordinary encapsulated empyema had been entered. Dr. Benjamin Castleman was called, and a frozen section on a specimen from the abscess wall confirmed the presence of inflammatory tissue and the absence of malignant tissue. The patient made a rapid, uneventful recovery from this encapsulated empyema.

DR. KING: What was the organism?

DR. ADAMS: Both alpha and beta hemolytic streptococci were grown on culture.

DR. MALLORY: The biopsied specimen from the deep wall of the cavity showed an organizing pneumonitis underneath a lot of fibrous tissue and granulation tissue.

DR. ADAMS: This case was shown to several notable men in the thoracic field during the summer, and no one has yet made the correct diagnosis.

DR. KING: Dr. Churchill did.

DR. CHURCHILL: I merely raised the question.

DR. HAMPTON: He had no responsibility.

CASE 26452

Presentation of Case

A thirty-year-old single woman entered the hospital complaining of shortness of breath and a chronic cough associated with sputum.

Because of the patient's poor condition the history was obtained from her sister. In another hospital, three years before admission, the patient had had a right radical mastectomy for carcinoma of the breast, followed by x-ray sterilization. Monthly x-ray examinations for the ensuing half year were negative. Two and a half years before admission the patient caught cold and developed a cough. Her physician said that she had "bubbles" in the chest, and although she continued to work for the next two weeks, the cold became much worse and she felt delirious and feverish. Her physician then made a diagnosis of pneumonia, and she remained in bed for the next month. After this illness she remained well until two years before entry, when she again caught cold, developed a cough with yellow sputum, a "rubbing" pain in the chest and a temperature of 103°F. She was treated with adrenalin, a cough medicine, codeine, a chest binder and sulfapyridine for the next month, but the cough persisted. Five months before admission she developed marked shortness of breath on exertion, was compelled to rest three or four times when climbing a flight of stairs and needed two pillows at night. She became easily fatigued and exhausted, and noticed "skipped" beats in the heart. A paroxysmal cough occasionally produced yellow sputum. An electrocardiographic recording three months before admission was normal, but an x-ray examination two months later revealed "fluid in the chest." On the same day a paroxysm of coughing produced blood-streaked sputum, and later the patient brought up a dark red clot. The next morning she entered another hospital, where a chest tap yielded one quart of lemon-colored fluid from the left side. This was repeated one week later, but "only a little blood" was obtained. Two and a half weeks before entry, sulfapyridine therapy was instituted, but discontinued because of nausea and vomiting. Five days later the patient was given sulfathiazole, which was continued for one week. Four days before entry she left the hospital and remained at home without medical care until the time of admission.

The family history and past illnesses were irrelevant.

Physical examination showed the patient to be dehydrated, toxic and acutely ill. The right breast had been amputated. The fingers were clubbed, and the nails showed an increased curvature. The tongue was dry and coated. Examination of the heart was negative; the blood pressure was 120 systolic, 72 diastolic. The left chest was flat to percussion, with a point of maximum dullness at the angle of the scapula. Breath sounds were absent over the lower half of this side of the chest. The liver was palpable two fingerbreadths below the costal margin.

The temperature was 101.6°F., the pulse 126, and the respirations 28.

Examination of the urine showed a + test for albumin. No sputum could be obtained for examination. Examination of the blood showed a red-cell count of 2,920,000 with a hemoglobin of 7.8 gm. (photoelectric-cell technic), and a white-cell count of 9000. A blood Hinton test was negative.

X-ray examination of the chest showed a normal lung and diaphragm on the right side. The left side of the diaphragm — demonstrated by a gas bubble in the stomach, but not seen at its upper border — was slightly elevated. There was density in the entire area of the left lower lobe, which was homogeneous except in its central portion, where there was an irregular cavity. The cavity appeared to be near the center of the lobe. No fluid level was demonstrated.

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. Edward D. Churchill: We have no x-ray report from six months after the cancer of the breast was removed to a date two months before admission — a period of two to three years.

As we read the story up to the physical examination I think that we are, of course, following the lead that is offered by the preceding history of cancer of the breast and thinking seriously of pulmonary metastases. The patient, when she entered the hospital, complained of chronic cough associated with sputum, but there is no note regarding the sputum, and, of course, we should be interested to know whether the sputum was putrid or bloody and what the microscopic examination showed.

What might this be? First of all, metastasis of cancer of the breast. Metastatic cancer of the lung rarely produces bloody sputum, or clubbing of the fingers unless a large bronchus is blocked. The strict localization of the disease to one region, with a clear opposite lung, is against metastases from a cancer of the breast. Dr. George W. Holmes's advice is always in my mind; namely, that a past history of cancer will lead one astray just as often as it will put one on the right track. I am therefore going to exclude a metastatic lesion from the breast from my list of preferred diag-

noses. However, we know that the behavior of cancer is unpredictable, and the tradition in these exercises is to fit everything together in one diagnosis.

This might be a primary tumor of the lung. The past history of cancer probably makes it even more likely that this patient would have a primary tumor of the lung than would a random representative of the general population. The history is consistent with a primary lesion of the lung. We may cheat a bit and say that the surgeon in charge probably would have bronchoscoped the patient instead of operating if he had thought that it was a primary tumor of the lung — but he might not have arrived at the correct diagnosis himself.

I am afraid that for practical purposes I have to come down to a diagnosis of empyema. I do not know when it started. It might have started with the second attack of pneumonia — when the patient had the "rubbing" pain in the chest. We have in the record a history of fluid that was aspirated and described as lemon-colored — a quart of it. That might have gone on and thickened to form the empyema, or there might have been a separate pocket of localized empyema that was never reached by any tap. The basal situation of this lesion suggests the so-called "infrapneumonic type" of empyema that lies between the lower lobe and the diaphragm. The clubbing of the fingers does not usually occur with encapsulated empyema unless a bronchial fistula develops, and then we commonly see pulmonary osteoarthropathy. If a patient has an empyema and has been coughing and raising yellow sputum, it is fair to assume that a bronchial fistula and clubbing of the fingers might follow. The absent breath sounds are not typical of empyema. We should expect a diminished bronchial breathing. However, with marked fixation of the diaphragm and a splinting of the chest wall, bronchial breathing may often be so distant that it is described as absent. There was probably some diminished excursion of the chest, as indicated by a narrowing of the intercostal spaces. If we had been privileged to examine the patient at the time this x-ray film was taken, we should have observed that she was not moving the lower portion of the left chest. That again indicates pleural involvement and pleural infection. Against the hypothesis of an empyema is the position of the shadow, which is described as being near the center of the lobe. Dr. Hampton, this is not a true lateral film, but as you can see, is somewhat oblique, throwing the left side quite a bit forward. Might not the cavity be peripheral?

DR. AUBREY O. HAMPTON: That is a portable film and the apparent rotation is due to magnification. I should not think it is as much rotated as you at first thought. One must localize the cavity in a position away from the chest wall.

DR. CHURCHILL: And deep within the chest. Whether it is within the lobe is another thing. They went too far with that, did they not?

DR. HAMPTON: It is in the lower lobe.

DR. CHURCHILL: It appears to occupy the region where the lobe commonly lies.

DR. HAMPTON: That is a more accurate statement.

DR. CHURCHILL: I am going to make a diagnosis of encapsulated empyema with a bronchial fistula.

DR. HAMPTON: Complete consolidation in the left lower lobe gives a picture exactly like fluid — the same shape and everything.

DR. DONALD S. KING: But not displaced mediastinum.

DR. HAMPTON: The patient has scoliosis. Perhaps she had it before this illness.

DR. CHURCHILL: I shall make a diagnosis of encapsulated empyema.

Without hedging I want to call attention to something I think we have perhaps forgotten in this case, and certainly in the case Dr. King discussed — it is an old trick that the late Dr. William H. Smith taught me in examining the sputum in a case of long-standing encapsulated empyema draining into a bronchus. He always maintained that a pocket of pus in the pleura will for a long period retain its bacteriological purity. In the case Dr. King discussed, examination of the sputum, if it had been done by smear and gram stain, might have revealed a clear-cut predominance of chains of streptococci. Of course we should like that type of information in this case. The empyema may have been due to a streptococcus or to some other organism, but it is the predominance of any one organism in the smear of the sputum that may give you the lead.

DR. TRACY B. MALLORY: Perhaps Dr. Davenport can give us more exact information.

DR. LOWREY F. DAVENPORT: The patient was coughing but not raising anything, and consequently had no sputum to be examined at the time she came in. When we tapped the posterior chest below the angle of the scapula and obtained frank pus we reasoned about the case as Dr. Churchill has. By tying together the previous history of pneumonia, the lemon-colored fluid and the finding of pneumococci in the pus, we thought we were safe in assuming that this was an encapsulated pneumococcal empyema. It was with that

diagnosis that the patient was transferred for rib resection.

DR. CHURCHILL: How much pus did you obtain from the chest tap? Was it a free flow or a very small amount?

DR. DAVENPORT: I recall that about 60 cc. of frank pus was removed.

DR. CHURCHILL: Of course, one can get a small amount of pus from tapping a drowned lung, but with the added information of 60 cc. of freely flowing pus, I should certainly be on the side of the surgeon who operated with the diagnosis of encapsulated empyema.

DR. KING: That seems easy.

DR. RALPH ADAMS: Do you mean that you agree, Dr. King?

DR. KING: I do not see how I can make any other diagnosis.

DR. HAMPTON: How do you explain the fact that the cavity was in the center of the lobe, away from the chest wall and near the center of the dense shadow?

DR. KING: It remains to be proved that it was in the lung.

DR. DAVENPORT: In doing the chest tap I believed that I was going through a very thick pleura.

DR. ADAMS: The diagnosis of encapsulated empyema was apparently confirmed at operation, and thick pus, in addition to what Dr. Davenport removed, was evacuated. The pleura was greatly thickened. In the base of the empyema cavity the tissue was irregular and necrotic, somewhat different from that which lined the remainder of the cavity. We did not know how to interpret it, and we therefore put a tube into the cavity, as is usually done for such cases. The following morning the patient began to lose air through the tube, which was indicative of a bronchial fistula. That did not occur until twelve hours after the operation. Still later, she began to cough up some blood, and the temperature rose rapidly. She died the following day.

DR. MALLORY: Is there anything of interest in the post-mortem films?

DR. HAMPTON: I should like to show that Dr. Adams put the tube directly into the cavity that the films had demonstrated.

CLINICAL DIAGNOSIS

Encapsulated empyema.

DR. CHURCHILL'S DIAGNOSIS

Encapsulated empyema, with bronchial fistula.

ANATOMICAL DIAGNOSES

Carcinoma, metastatic, of bronchus, lung, bronchial lymph nodes, mediastinum and pleura.
Lobar pneumonia, Type 3 pneumococcus, left lower lobe, unresolved.
Lung abscess, acute, left lower lobe.
Pleuritis, chronic fibrous and acute fibrinous, left.
Pulmonary edema, slight, right lower lobe.
Arteriosclerosis, moderate, coronary.
Operative scar: right radical mastectomy; left thoracotomy.
Osteoarthropathy of fingers.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy it was apparent that all the pathologic lesions had not been revealed at operation. We could identify no empyema cavity. The lower lobe on the left felt solid on external palpation, but on cutting into it a large central abscess cavity was found, nearly 4 cm. in diameter. Dr. Adams's drainage tube lay in this cavity, the walls of which varied in consistence. The lower and lateral portions were somewhat soft but tough, and evidently consisted of organized lung tissue — an organizing pneumonitis. On the upper and medial surfaces the walls were relatively hard, and it was at once apparent that this was metastatic tumor. The carcinomatous mass involved chiefly the apex of the lower lobe, surrounding all the bronchi and markedly narrowing the lumens, without invading any bronchus, however. There were three bronchi that communicated with the abscess cavity. The tumor had also extended into the mediastinal nodes, where a large mass of tumor tissue was also found. We did not find any other spots of metastatic tumor in the post-mortem examination, in either the upper lobe or the opposite lung. The abscess fluid at autopsy was not foul, and the process was apparently still a pure pneumococcal infection.

DR. CHURCHILL: Did the cancer cause the empyema, or was it an incidental finding?

DR. MALLORY: It had certainly caused bronchial stenosis, and I think it is fair to assume with infection of the lung that the stenosis might have prevented normal resolution of a coincidental pneumococcal pneumonia.

DR. HAMPTON: How many lung abscesses have you seen due to metastatic cancer?

DR. MALLORY: Offhand I do not remember any other. It very commonly results from bronchiogenic carcinoma, of course.

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THE WILL TO LEARN

Three weeks ago the Interstate Postgraduate Medical Association of North America held its five-day annual meeting at Cleveland. The public auditorium, an enormous hall with a seating capacity of thousands, was hired for the purposes of the daily assembly and the housing of the commercial and scientific exhibits. Five thousand physicians were registered. The majority came from the Midwest but many were from communities as distant as Texas, California and Canada. They met every morning at eight o'clock, and adjourned at nine or ten o'clock at night, having had an hour's respite for both lunch and dinner. Every paper and presentation was started and stopped on the minute. The program was general and had a wide medical appeal. The association first met in a small church a number of years ago and has steadily grown, until last year at the Chicago meeting the attendance was six thousand. Such an extraordinary demonstration of the will to learn on the part of the medical profession at large may well be regarded as indisputable evidence that the health problems of the western three quarters of North America are in good hands and that the community at large need have no fear for its well-being. It is perhaps not saying too much to state also that this meeting is evidence of a type of altruistic humanism and humanitarianism that will in the end serve to lead the world out of its present chaotic barbarianism.

Next week, New England has her third postgraduate assembly, modeled on the larger organization but cut down to fit a smaller territory and fewer doctors. Every registered physician in this area has been invited to attend. The appeal is universal rather than specialized, and the conduct of the meeting may be expected to reach the high efficiency of its predecessors. There can be no question of the will to learn on the part of the local profession; therefore, let them compliment the speakers, evidence their faith in the managing committee and profit their own interests by attending in even larger numbers than they have in the past two years.

THE COURT OF LAST APPEAL

The comparative value of different methods for the demonstration of tubercle bacilli has been well shown by Pinner and Wooley[1] in their study of 239 specimens of sputum from tuberculous patients, all of which were reported "negative" on direct smear. Further search for tubercle bacilli in these same specimens by other methods revealed that no less than 10 per cent were positive by the sputum-concentration technic, 56 per cent by culture, and 77 per cent by guinea-pig inoculation. These figures show clearly that the unqualified term "negative sputum" is practically meaningless.

The absence of sputum in children led to the study of the gastric contents as a source of tubercle bacilli. Meunier in 1898 opened the way for this method in the diagnosis of tuberculous pulmonary lesions. Since then, aspiration of the fasting stomach contents has become well established as a noteworthy procedure for the di-

agnosis of primary and reinfection types of tuberculosis in infants and children. Recently this technic has been applied to adults. Sweany and his co-workers[2] believe that it is better than any other method in establishing active tuberculous foci. They further state that "no patient with clinical signs of tuberculosis who has negative sputum should be considered negative for the disease until stomach lavage has yielded negative results."

Stiehm[3] has presented an excellent study of 70 cases of subclinical tuberculosis that presented x-ray evidence of small pulmonary infiltrations. Usually there was no expectoration, and sputum, when present, was negative in every case by direct smear. As Pinner and Wooley concluded from their figures for sputum, Stiehm found that injection of the fasting gastric contents into guinea pigs was the most reliable method of proving the activity of these small lesions. The repeated presence of tubercle bacilli in the gastric contents of the subclinical cases usually indicated an unfavorable course, whereas their repeated absence gave almost complete assurance of a favorable outcome. A change of the gastric contents from positive to negative was a favorable prognostic sign. He found that sedimentation rates, white-cell counts and differential counts were significantly unreliable signs in these early cases.

Stiehm's method for examining the gastric contents of adults consists in the aspiration of fasting specimens on three successive mornings, by means of a catheter passed through the nose. Ten to 15 cc. of stomach contents is usually withdrawn, but if nothing is obtained 15 cc. of sterile physiological salt solution is injected into the stomach and withdrawn fifteen minutes later. Following centrifugation, the sediment is examined by direct smear and is injected into a guinea pig in each case. In Stiehm's series of 40 cases with questionable lesions and "negative" or absent sputums, direct smears of sediments from the gastric contents were positive in 18 per cent, whereas guinea-pig inoculations were positive in 72 per cent.

These figures are worthy of respect and deserve more widespread application. They point to a simple procedure that appears to contribute enormously not only to the accuracy of diagnosis in early tuberculosis but also to the means of determining the activity of minimal and subclinical lesions. Gastric lavage, when properly performed, is a procedure that may well be termed the "court of last appeal" in the search for tubercle bacilli.

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MEDICAL EPONYM

ESMARCH BANDAGE

Johann Friedrich August von Esmarch (1823–1908), professor of surgery at Kiel, published a little booklet *Der erste Verband auf dem Schlachtfelde* [The First Bandage for Use on the Battlefield] (Kiel: Schwers'sche Buchhandlung, 1869). A sample of the bandage was pasted in the back of the book. The following translated description appears on page 9:

> A three-cornered cloth of suitable size would be the best material for use as the first bandage on the battlefield. . . .
>
> If one were to choose for the preparation of these cloths a very light-weight cotton shirting, one yard in width, and, if they were manufactured in large quantities, each one would cost only a few cents.
>
> Such a cloth can be folded to the size of a playing card, and when pinned together with two or three large pins,—perhaps two inches long,—is about half an inch thick and weighs hardly an ounce, at any rate less than the bandage now carried by the soldier in his haversack.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

NEW ENGLAND POSTGRADUATE ASSEMBLY

The third New England Postgraduate Assembly will be held on November 13 and 14 at Sanders Theatre, Harvard University, Cambridge. Buffet luncheons will be served in Memorial Hall on both days. The dinner on Wednesday evening will be followed by a talk by Dr. Harrison S. Martland, of Newark, New Jersey, his subject being "Dr. Watson and Mr. Sherlock Holmes." The registration fee ($3.00) does not include admission to the luncheons (75 cents) or the dinner ($1.25). Those desiring luncheon or dinner

tickets should apply immediately, if they have not already done so, to the Postgraduate Assembly Committee, 8 Fenway, Boston. Such applications should be accompanied by a check or money order, and if they are received by the committee during the week of the assembly, the applicant must claim his badge and tickets at the registration desk.

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

223
40

DIABETIC COMA ASSOCIATED WITH DELIVERY

Mrs. F. G., a nineteen-year-old primipara, known to have had diabetes for eleven years, was first seen with acute pyelitis on July 24, 1932, when six and a half months pregnant.

The family history was noncontributory. The patient's past history was irrelevant except for the diabetes. She had a diabetic retinitis. Catamenia began at twelve, were regular with a twenty-eight-day cycle, and lasted five days The last period began on January 14, making her expected date of confinement October 21 to 27.

Physical examination showed a very well-developed young woman. The heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The blood pressure was 122 systolic, 60 diastolic. Examination of the extremities was negative. The uterus was enlarged to a size corresponding to a pregnancy of twenty-six to twenty-seven weeks. There was tenderness in the region of the right costovertebral angle, and the urine was full of pus. Temperature had been ranging from 99 to 104°F. A diagnosis of pyelitis was made, but under conservative treatment it cleared up; the patient went on to term without an exacerbation.

On October 1 she was sent to the hospital. The weight was 136 pounds. The blood pressure was 110 systolic. Examination of the urine showed a slight trace of albumin, but there was no edema. The diabetes was well controlled. The uterus was big, and the fetal heart was audible. Vaginal examination showed the tissues to be soft, the cervix not obliterated and not open. The patient remained in the hospital until she started in spontaneous labor.

On October 8 vaginal examination was performed. The cervix was very soft and dilated to admit one finger, but the canal was rather long. It was planned to induce labor in another week.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

On October 13 she started in labor. Examination at 8:30 a.m. revealed a very soft cervix, dilated to admit two fingers but not flat. The membranes were ruptured, and 2 minims of posterior pituitary extract was given. At 10:00 a.m. the patient became unconscious. A specialist in diabetes was immediately summoned, and intensive treatment for the coma was instituted. At this time several examiners heard the fetal heart. A note says that at 9:00 p.m., when the cervix was dilated to admit four to five fingers, with the head well engaged, the fetal heart was audible. At 10:00 p.m. on October 13, after full dilatation, a baby weighing 9 pounds, 6 ounces, with beginning maceration, was delivered by a single forceps operation. Between noon on October 13, just after the patient went into coma, and noon on October 14, 300 units of insulin was given.

The convalescence was normal and satisfactory except for an attack of pyelitis that cleared up very quickly.

Comment. This case illustrates many things. In the first place this young woman was what is called an "insulin" diabetic patient. Diabetes developed at the age of eight years, and the patient would not have lived to reach maturity and to become pregnant had it not been for insulin.

This patient was hospitalized two weeks before spontaneous labor occurred at approximately thirty-eight weeks, and although she was under adequate treatment, coma developed shortly after the onset of labor. A specialist in diabetes, had one been in attendance, might well have appreciated the onset of coma. This emphasizes the need for having such a specialist present during all diabetic labors so that blood sugar tests may be done frequently, and impending coma diagnosed in time to prevent actual unconsciousness.

This case illustrates the danger of allowing patients with severe diabetes to go to spontaneous labor after viability. A cesarean section done any time before labor started would have produced a live child — one that in all probability would have survived. This case also illustrates the size of babies born of diabetic mothers and also how quickly maceration can occur. It is possible that the fetal heart was not heard at 9:00 p.m., but it is a fact observed by several different people that the fetal heart was audible at 10:00 a.m.

In a subsequent pregnancy this patient was aborted.

Until diabetes in pregnancy can be controlled better than it is at present, any patient with severe diabetes who goes beyond thirty-seven weeks with a viable child stands a definite chance of losing the fetus by intrauterine death unless labor is induced or a cesarean section performed.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning November 11:

BARNSTABLE

Sunday, November 17, at 4:00 p.m., at the Cape Cod Hospital, Hyannis. Pediatric Case Discussions. Instructor: Louis K. Diamond. Donald E. Higgins, *Chairman.*

BRISTOL NORTH

Friday, November 15, at 4:00 p.m., at the Morton Hospital, Taunton. Acute Abdominal Pain: Its interpretation and management. Instructor: Richard B. Cattell. Lester E. Butler, *Chairman.*

BRISTOL SOUTH (New Bedford Section)

Friday, November 15, at 4:00 p.m., at St. Luke's Hospital, New Bedford. The Treatment of Varicose Veins. Instructor: Robert R. Linton. Robert H. Goodwin, *Chairman.*

ESSEX NORTH

Friday, November 15, at 4:30 p.m., at the Clover Hill Hospital, Lawrence. Obstetrical Complications with Case Histories and Clinical Problems. Instructor: Judson A. Smith. John Parr, *Chairman.*

ESSEX SOUTH

Tuesday, November 12, at 4:00 p.m., in the Conference Room, Salem Hospital, Salem. Nutritional Deficiencies and the Uses of Preparations of Vitamins. Instructor: Maurice B. Strauss. J. Robert Shaughnessy, *Chairman.*

MIDDLESEX NORTH

Friday, November 15, at 5:00 p.m., at St. John's Hospital, Lowell. Recent Advances in Medical Therapeutics. Instructor: Charles L. Short. William S. Lawler, *Chairman.*

PLYMOUTH

Tuesday, November 12, at 4:30 p.m., in the Nurses' Home of the Brockton Hospital, Brockton. Pediatric Case Discussions. Instructor: Lewis W. Hill. Walter H. Pulsifer, *Chairman.*

COMMITTEE ON INDUSTRIAL HEALTH

Explosion Hazards in Storage-Battery Rooms

The results of a study of explosion hazards in storage-battery rooms are given in a report just issued by the Bureau of Mines, United States Department of the Interior. The study grew out of a co-operative investigation between the Bureau of Mines, the Boston Edison Company and the Boston Consolidated Gas Company which has been in force for a number of years and has been carried out primarily for the purpose of determining the explosion hazards in manholes, conduits and other unventilated spaces underground. Surveys were made in connection with this investigation to determine and eliminate the hazards due to hydrogen in the many large standby-type storage-battery rooms of one of the co-operative companies.

This report gives the average and maximum concentrations of hydrogen present in twenty-three battery rooms when the batteries were being charged and when the batteries were idle ("on float"). The battery rooms were all comparatively large, the volume of free air space in the rooms ranging from 13,445 to 86,678 cubic feet, and the number of cells in each installation varying from 82 to 344. Two or more surveys were made in each battery room during the investigation, covering a period of about four years. Approximately 5000 samples of battery-room atmospheres were taken and analyzed.

The investigation showed that the concentration of hydrogen in battery rooms was low and that no hazards were involved when the batteries were idle. Under this condition, the concentrations of hydrogen varied from zero to a maximum of 0.29 per cent. The only cases where hazardous concentrations of hydrogen were present were during the periods when the batteries were being charged and more especially toward the end of the charging period. The highest average concentration of hydrogen in any battery room tested was 5.35 per cent and was in the explosive range of hydrogen-air mixtures.

The results showed rather definitely that mechanical ventilation is the more satisfactory method of ventilation because the concentration of the hydrogen in the rooms ventilated by natural means averaged 50 per cent higher than that in rooms provided with mechanical ventilation. The charging rate was purposely changed during many of the surveys, and these results showed that in general the average hydrogen concentration found in the rooms was approximately proportional to the charging rate.

Although the information given in the report applies to certain battery rooms of one company, specific information relative to the details of the battery rooms, the cells and the ventilation equipment is given so that the results may be applied to various spaces in which hydrogen is liberated by electrolytic processes.

This report, described as Bureau of Mines Technical Paper No. 612, "Explosion Hazards in Storage Battery Rooms," by G. W. Jones, John Campbell, R. E. Dillon and O. B. Benson, may be purchased from the Superintendent of Documents, Government Printing Office, Washington, D. C., at a price of 10 cents.

DEATHS

CARLETON — Ralph Carleton, M.D., of Springfield, died October 26. He was in his seventy-first year.

Born in Norwich, Connecticut, he received his degree from the Harvard Medical School in 1894. He served as an intern at the Carney Hospital and the Massachusetts Eye and Ear Infirmary in Boston before starting private practice in Springfield. Dr. Carleton was on the staff of the Springfield Hospital and was a fellow of the Massachusetts Medical Society and the American Medical Association. He held memberships in the American Academy of Ophthalmology and Oto-Laryngology, the New England Ophthalmological Society, the Springfield Academy of Medicine and the Springfield Medical Club.

His widow survives him.

HILL — George J. Hill, M.D., of Boston, died October 29. He was in his sixty-second year.

Born in Beverly, he attended Noble and Greenough School and received his degree from the Harvard Medical School in 1903. He also studied at the University of Berlin. Dr. Hill was then surgeon for the United Shoe Machinery Corporation in Beverly for fifteen years. In 1918, he moved to Boston, where he was a pediatrician on the

staff of the Children's Hospital.

Dr. Hill was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a brother, two sons, a daughter and four grandchildren survive him.

NOWELL — Howard W. Nowell, M.D., of Brookline, died October 28. He was in his sixty-ninth year.

Born in Merrimacport, he attended Lyndon College and received his degree from Boston University School of Medicine in 1911. He was a former pathologist at the Massachusetts Homeopathic Hospital and was instructor in pathology from 1911 to 1913 and then associate professor of pathology from 1913 to 1915 at Boston University School of Medicine. Dr. Nowell was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

PARKER — Raymond B. Parker, M.D., of Winthrop, died October 19. He was in his fifty-sixth year.

Dr. Parker was born at Reading and attended Dartmouth College, receiving his degree from Harvard Medical School in 1912. He interned at the Boston City and Boston Lying-in hospitals, and was later house physician at the Boston Lying-in Hospital. From 1914 to 1915 he was instructor in obstetrics at the Harvard Medical School. A former chairman of the Winthrop Board of Health, he was also school physician there for twenty years.

Dr. Parker was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, his mother, a daughter, a son and a sister survive him.

MISCELLANY

NATIONAL HEALTH LIBRARY

The National Health Library, which completed two decades of service this year, announces its removal from the RCA Building in Rockefeller Center to 1790 Broadway, New York City. Since its establishment twenty years ago, this library has brought together one of the best collections of source material in the United States on public health, sanitation, health education and related subjects. It includes 6000 volumes and 30,000 pamphlets. More than 500 medical and public-health periodicals are received regularly from all parts of the world.

Administered by the National Health Council, the library is intended primarily for the use of the seventeen health organizations that are members of the council. Persons who are not members of the supporting organizations may have the privilege of using the library by paying a small annual fee.

Members from all over the country avail themselves of the privilege of borrowing books from the library. Nurses and public-health workers in small towns in which there are no libraries are especially grateful for the service. Material may be found at the National Health Library that might take days and even weeks to unearth elsewhere. The indexing of this material makes it of especial value for research workers.

To make the current material useful, all periodicals are indexed in a card catalog. Every week a mimeographed list of the more important articles is issued under the title, *The Library Index: A weekly index to current periodical literature in the field of public health*. This publication is available to the public for a small annual subscription.

The National Health Council includes the following active member agencies: American Society for the Hard of Hearing, American Heart Association, American Public Health Association, American Red Cross, American Social Hygiene Association, American Society for the Control of Cancer, Conference of State and Provincial Health Authorities of North America, Maternity Center Association, National Committee of Health Council Executives, National Committee for Mental Hygiene, National Organization for Public Health Nursing, National Society for the Prevention of Blindness and the National Tuberculosis Association. The United States Children's Bureau and the United States Public Health Service are advisory members of the council. The American Nurses' Association and the Foundation for Positive Health are associate members.

VITAMIN-FREE FOODS

A recent announcement by the research laboratories of the S. M. A. Corporation reveals that they are now in a position to provide vitamin-free casein and other vitamin-free foods to research workers who have previously been obliged to manufacture these items.

For many years the company's research laboratories have been producing these foods exclusively for their own use. With expansion of their facilities they are now able to provide vitamin-free foods to others at an exceptionally reasonable cost, and this should prove to be a great convenience to those who are engaged in this type of investigative work. Quantities of 1, 5, 10 or 100 pounds, or even more, may be ordered directly from the Research Laboratories, S. M. A. Corporation, Chagrin Falls, Ohio.

NOTES

Twenty-four appointments to the teaching and research staff of the Harvard Medical School were recently announced by the University as follows: (effective September 1, 1940) Edward A. Gall, M.D. Tulane '31, instructor in pathology; Thomas H. Weller, M.D. Harvard '40, teaching fellow in bacteriology; Kirk T. Mosley, M.P.H. Harvard '40, assistant in epidemiology; Joseph R. Frothingham, M.D. Harvard '37, assistant in medicine; Herbert I. Harris, M.D. Tufts '36, assistant in neurology; Earl S. Seale, M.D. Tulane '35, assistant in ophthalmology; Vincent G. Ryan, M.D. Yale '34, assistant in psychiatry; Elvin V. Semrad, M.D. University of Nebraska '34, assistant in psychiatry; Howard A. Bouve, M.D. Harvard '21, assistant in surgery; Lee G. Kendall, M.D. Harvard '30, assistant in surgery; Howard Ulfelder, M.D. Harvard '36, assistant in surgery; Alfred L. Florman, M.D. Johns Hopkins '38, research fellow in bacteriology; David E. Green, Ph.D. University of Cambridge, England, '34, research fellow in biological chemistry; Laurence E. Strong, Ph.D. Brown University '40, research fellow in physical chemistry; Isadore Fankuchen, Ph.D. Cornell '33, research fellow in physical chemistry; Carl C. Jensen, S.M. University of Nebraska '29, research fellow in physical chemistry; Donal Murnaghan, M.B., B.C.H., B.A.O., National University of Ireland '37, research fellow in medicine; George E. Hobbs, M.D. University of Toronto '33, research fellow in neurology; Charles C. Roby, Ph.D. University of Chicago '40, research fellow in obstetrics; Oliver H. Straus, M.D. Columbia '40, research fellow in pharmacology; Effren C. Del Pozo, M.D. National University of Mexico '36, research fellow in physiology; Harold I. Harvey, M.D. Duke University '37, research fellow in psychiatry; (effective November 1, 1940) Charles R. Harmison, Ph.D. University of Illinois '40, research fellow in physical chem-

istry; (effective January 1, 1941) Edwin L. Cantlon, M.D. Harvard '36, assistant in surgery.

Harvard University has recently announced the promotion of Dr. John E. Gordon, professor of preventive medicine and epidemiology at Harvard Medical School and director of the new Harvard Public Health Unit and Harvard–Red Cross Hospital Unit in England, to Charles Wilder Professor of Preventive Medicine and Epidemiology. This professorship, held by Dr. Hans Zinsser as head of the Department of Bacteriology and Immunology from 1935 until the time of his death this fall, now returns to the department to which it was originally allocated, Dr. Milton J. Rosenau, of the Department of Preventive Medicine and Epidemiology, having been the holder of the chair from its founding in 1909 until his retirement in 1935.

CORRESPONDENCE

ARMY MEDICAL LIBRARY

To the Editor: I am directed by the Surgeon General to inform you that authors' reprints are gratefully received at the Army Medical Library. They are placed in a special collection catalogued by author and thus form a ready bibliography of the work of any given writer and a valuable supplementary source of material when the volume of original publication is temporarily unavailable at the bindery or on loan.

HAROLD W. JONES, *Librarian,*
Colonel, Medical Corps, United States Army.

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION, COUNCIL ON PHARMACY AND CHEMISTRY

To the Editor: In addition to the articles enumerated in our letter of September 4 the following have been accepted:

Abbott Laboratories
- Bismo-Cymol 60-cc. bottle
- Bismo-Cymol 500-cc. bottle
- Ampoules Procaine Hydrochloride, 1 per cent, W/V, 1.5 cc.
- Ampoules Procaine Hydrochloride, 1 per cent, – Epinephrine 1:50,000 Solution, 2 cc.
- Butyn Sulfate Tablets, 25 mg.

Cheplin Biological Laboratories
- Cheplin's Solution of Sodium Cacodylate with Benzyl Alcohol:
  - 0.05 gm. (¾ gr.), 30-cc. vial;
  - 0.2 gm. (3 gr.), 30-cc vial;
  - 0.3 gm. (5 gr.), 30-cc. vial;
  - 0.5 gm. (7½ gr.), 30-cc. vial;
  - 0.065 gm. (1 gr.), 1 cc.

Endo Products, Incorporated
- Ampoules Mercury Succinimide, 0.01 gm. (⅙ gr.), 1 cc.
- Ampoules Sodium Thiosulfate Solution, 0.5 gm. in 5 cc.
- Ampoules Sodium Thiosulfate Solution, 1.0 gm. in 10 cc.
- Tablets Sulfanilamide — Endo, 5 gr.
- Tablets Sulfanilamide — Endo 7½ gr.

The National Drug Co.
- Parenteral Solution of Liver, 10-cc. ampul vials, 5 *U.S.P.* injectable units per cc.
- Parenteral Solution of Liver, 10-cc. ampul vials, 10 *U.S.P.* injectable units per cc.

Parke, Davis and Company
- Capsules Sulfapyridine, 0.25 gm. (3¾ gr.)

Riedel-de Haen, Incorporated
- Pernoston Sodium
  - Ampules Pernoston Sodium, 10 per cent. 2 cc.

Smith-Dorsey Company
- Phenobarbital Tablets, 0.1 gm. (1½ gr.)
- Tablets Aminophyllin, 0.1 gm. (1½ gr.)

Frederick Stearns and Company
- Tablets Thiamine Hydrochloride, 5 mg.
- Tablets Thiamine Hydrochloride, 10 mg.

E. R. Squibb and Sons
- Solution Thiamine Chloride — Squibb, 5-cc. vial, 100 mg. per cc.

Upjohn Company
- Hypodermic Tablets Procaine Hydrochloride, 0.05 gm.
- Hypodermic Tablets Procaine Hydrochloride, 0.02 gm. (⅓ gr.), with Epinephrine, 0.025 mg. (1/2500 gr).

PAUL NICHOLAS LEECH, *Secretary.*
535 North Dearborn Street,
Chicago, Illinois.

NOTICES

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic at the Peter Bent Brigham Hospital will be held on Wednesday, November 13, from 2:00 to 4:00 p.m. Drs. Edward S. Emery and Robert Zollinger will speak, their subject being "Diarrhea and Constipation." A clinicopathological conference, conducted by Dr. Elliott C. Cutler, will take place from 4:00 to 5:00 p.m.

Physicians and students are cordially invited to attend.

BOSTON GASTRO-ENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastro-Enterological Society will be held in the Carney Hospital Auditorium on Wednesday, November 13, at 12:00 m.

PROGRAM

- Necessity of Surgical Intervention in Intractable Peptic Ulcers. Dr. William E. Browne. Discussed by Dr. Norman A. Welch.
- Physiological Rest in the Treatment of Diabetes. Dr. Charles W. Finnerty. Discussed by Dr. G. Herbert Cleary.
- Gastrointestinal Symptoms in Urologic Disease. Dr. Francis J. West. Discussed by Dr. C. J. E. Kickham.

BOSTON ORTHOPEDIC CLUB

The next meeting of the Boston Orthopedic Club will be held in Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Monday, November 18, at 8:00 p.m. Dr. Fritz Teal, of Lincoln, Nebraska, will speak on "The Orr Treatment of Compound Fractures."

Regular monthly meetings of the Boston Orthopedic Club will be held on the third Monday of every month until May 19.

GREATER BOSTON MEDICAL SOCIETY

There will be a meeting of the Greater Boston Medical Society in the auditorium of the Beth Israel Hospital on Tuesday, November 12, at 8:15 p.m. Dr. Austin M. Brues will speak on "Recent Advances in the Study of Cancer." Drs. Harry F. Friedman and Waldo E. Cohn will discuss the subject.

CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the Carney Hospital will be held in the auditorium of the Carney Hospital on Monday, November 18, at 11:30 a.m.

PROGRAM

Business meeting.
Case reports.
A New Method of Blood Transfusion: A demonstration.

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HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, November 12, at 8:15 p.m.

PROGRAM

Presentation of cases.
The Army in 1941: Contemplated military progress. Lt. Col. W. A. Collier, G.S.C.
The Practice of Medicine in the Army. Lt. Col. O. H. Stanley, M.C., U. S. A.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, former concertmaster with the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

MASSACHUSETTS EYE AND EAR ALUMNI ASSOCIATION

The annual meeting of the Massachusetts Eye and Ear Alumni Association, held in conjunction with the New England Ophthalmological and the New England Oto-Laryngological societies, will take place on Tuesday and Wednesday, November 12 and 13. The annual meeting and dinner (informal) will be held at the University Club on Wednesday evening, beginning with refreshments and a social gathering at 6:00 p.m.

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

A mental health conference, sponsored by the Essex South District Medical Society and eight other Massachusetts organizations, will be held on Friday, November 15, at the Hotel Hawthorne, Salem, at 9:30 a.m. Luncheon will be served at 1:00 p.m. Dr. Harry C. Solomon will speak on "Diagnosis and Treatment of Mental Disorders."

MASSACHUSETTS TUBERCULOSIS LEAGUE

The midyear meeting of the Massachusetts Tuberculosis League will be held at the University Club, 40 Trinity Place, Boston, on Thursday, November 14. The theme of the meeting concerns rehabilitation of the tuberculous.

At 10:00 in the morning, Dr. O. S. Pettingill will lead a round-table discussion on rehabilitation cases, and at 11:00 Miss Mabel M. Brown will be chairman of a round-table discussion on employment problems of the tuberculous. Outstanding authorities from the Massachusetts Employment Service, the Division of Vocational Rehabilitation, the Massachusetts National Youth Administration and other agencies will take part in the latter.

At 12:30, luncheon will be served, the charge being $1.00 per person. The principal speaker will be Miss Jessamine S. Whitney, statistician of the National Tuberculosis Association, who will discuss what is happening to tuberculous patients five years after their discharge from sanatoriums. Since these results include figures from eight Massachusetts sanatoriums and other agencies and organizations, they should be of exceptional value to Massachusetts physicians.

All interested persons are cordially invited to attend the meeting. Reservations can be made by telephoning (HAN 5480) or writing to the office of the Massachusetts Tuberculosis League, 1148 Little Building, Boston.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 p.m. Formal notice of the place of examination will be sent to each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the secretary's office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held in June, 1941.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire board, meeting at Cleveland, Ohio, from May 28 to June 1, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A, Part II examinations must be on file in the secretary's office not later than March 15, 1941.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The board announces a modification of the case-record ruling (effective January 1, 1942) as it appears in the September, 1940, issue of the booklet issued by the board. This ruling should read: "It is preferable that the number of cases submitted should not be more than half (25) of the total number of fifty (50) cases required."

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

UNITED STATES CIVIL SERVICE COMMISSION EXAMINATIONS

MEDICAL TECHNICIANS

Medical technicians experienced in surgical and x-ray work are needed by the War Department. The United States Civil Service Commission has announced an examination to fill these positions in the following grades and optional subjects: senior medical technician (roentgenology), $2000 a year; medical technician (roentgenology, and surgical), $1800 a year; assistant medical technician

(roentgenology, and surgical), $1620 a year. The salaries are subject to a retirement deduction of 3½ per cent.

Applications must be on file with the Commission's Washington office not later than November 28, if received from states east of Colorado and not later than December 1, 1940, if received from Colorado and states westward.

Applicants must have completed a four-year high-school course, unless they pass a written general test, and in addition, they must have had responsible experience in surgical duties in an operating room or clinic, or in x-ray work including x-ray photography and posturing, and in the installation and maintenance of x-ray apparatus. Appropriate college study may be substituted for part of the required experience. With the exception of those who have not completed the hign-school course, applicants will not be given a written test. All competitors will be rated on their qualifications as shown in their applications and on corroborative evidence.

Detailed information regarding the examinations and the proper application forms may be obtained from the Secretary of the United States Civil Service Examiners at any first-class or second-class post office or from the United States Civil Service Commission, Washington, D. C.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, November 10

Tuesday, November 12

Massachusetts Eye and Ear Alumni Association.

*9–10 a.m. Narcolepsy: A review and presentation of cases. Dr. W. F. Murphy. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

8 p.m. Mechanics of Gas Anesthesia. Dr. Albert Miller. New England Society of Anesthesiology. Boston City Hospital.

8:15 p.m. Harvard Medical Society. Peter Bent Brigham Hospital amphitheater.

8:15 p.m. Recent Advances in the Study of Cancer. Dr. Austin M. Brues. Greater Boston Medical Society. Beth Israel Hospital auditorium.

Wednesday, November 13

Massachusetts Eye and Ear Alumni Association.

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

12 m. Boston Gastro-Enterological Society. Carney Hospital auditorium.

*2–4 p.m. Diarrhea and Constipation. Drs. E. S. Emery and Robert Zollinger. Peter Bent Brigham Hospital.

Thursday, November 14

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9–10 a.m. Ovulation and the Effects of Pregnant Mares' Serum — Gonadogen (motion picture). Joseph H. Pratt Diagnostic Hospital.

*10 a.m. Massachusetts Tuberculosis League. University Club, 40 Trinity Place, Boston.

Friday, November 15

*9–10 a.m. Ménière's Disease. Dr. Donald Munro. Joseph H. Pratt Diagnostic Hospital.

Saturday, November 16

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

November 8, 15 and 22 — Thomas William Salmon Memorial Lectures. Page 692, issue of October 24.

November 12 — New England Society of Anesthesiology. Page 743, issue of October 31.

November 13 — Neisserian Medical Society of Massachusetts. Page 743, issue of October 31.

November 13 — United States Naval Hospital. Page 743, issue of October 31.

November 13, 14 — New England Postgraduate Assembly. Cambridge, Massachusetts.

November 14 — Pentucket Association of Physicians. Page 263, issue of August 15.

November 14 — American Conference on Industrial Health. Page 648, issue of October 17.

November 15 — Massachusetts Society for Mental Hygiene. Page 648, issue of October 17.

November 18 — Boston Orthopedic Club. Page 786.

November 18 — Monthly clinical meeting and luncheon. Carney Hospital. Page 787.

November 20 — Boston Society of Biologists. Page 742, issue of October 31.

December 10 — New England Society of Anesthesiology. Page 743, issue of October 31.

December 27–29 — National Convention of the Association of Medical Students, Boston.

January 4, 1941 — American Board of Obstetrics and Gynecology. Page 787.

March 8 — American Board of Ophthalmology. Page 201, issue of August 1.

April 21–25 — American College of Physicians. Page 1065, issue of June 20.

May 21, 22 — Massachusetts Medical Society, Boston.

June 2–6 — American Medical Association. Cleveland, Ohio.

District Medical Societies

ESSEX SOUTH

November 15 — Page 787.

FRANKLIN

November 12.

January 14.

March 11.

May 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

SUFFOLK

January 29 — Page 604, issue of October 10.

April 30 — Page 604, issue of October 10.

WORCESTER

November 13 — Grafton State Hospital, Grafton.

December 11 — St. Vincent Hospital, Worcester.

January 8, 1941 — Worcester City Hospital, Worcester.

February 12 — Worcester State Hospital, Worcester.

March 12 — Memorial Hospital, Worcester.

April 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOK REVIEW

The Vasometer System in Anoxia and Asphyxia: A study of the adjustment reactions of the mammalian organism. By Ernst Gellhorn, M.D., Ph.D. and Edward H. Lambert, M.D. 4°, paper, 71 pp., with 21 illustrations. Urbana, Illinois: The University of Illinois Press, 1939. $1.00.

This pamphlet is the result of a long series of experiments by Gellhorn and his associates at the University of Illinois. They have studied the effects on the central nervous system of oxygen-deficient gas mixtures, a condition that they define as "anoxia," and those of the same mixtures when combined with an increased carbon-dioxide tension in the blood, a condition that they define as "asphyxia." There is no clear distinction between anoxia and asphyxia in the medical literature, and the authors have carefully defined their use of these two words. The effects of the mixtures are measured in terms of the blood pressure of anesthetized dogs. They find that the effect of carbon dioxide is increased in anoxia, partly due to the weakening of the carotid-sinus pressor reflexes. Also, it is assumed that the intracellular metabolites formed during short periods of anoxia may interact with the effects of carbon dioxide.